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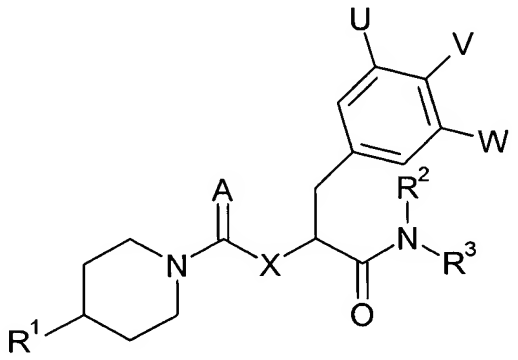
Selected CGRP antagonists, processes for preparing them and their use as pharmaceutical compositions

The present invention relates to CGRP antagonists of general formula



, (I)

the tautomers, diastereomers, enantiomers, hydrates, mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids, pharmaceutical compositions containing these compounds, the use thereof and processes for the preparation thereof.

In the above general formula (I) in a first embodiment

A denotes an oxygen or sulphur atom, a phenylsulphonylimino or cyanimino group,

X denotes an oxygen or sulphur atom, an imino group optionally substituted by a C_{1-6}-alkyl group or a methylene group optionally substituted by a C_{1-6}-alkyl group,

U denotes a C_{1-6}-alkyl group wherein each methylene group may be substituted by up to 2 fluorine atoms and each methyl group may be substituted by up to 3 fluorine atoms,

V denotes a chlorine or bromine atom, an amino, methylamino or hydroxy group,

W denotes a hydrogen, fluorine, chlorine, bromine or iodine atom, a difluoro- or trifluoromethyl group,

R^1 denotes a saturated, mono- or diunsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza or *S*,*S*-dioxido-thiadiaza heterocyclic group,

in which the abovementioned heterocycles are linked via a carbon or nitrogen atom,

contain one or two carbonyl or thiocarbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl group,

may be substituted at one or at two carbon atoms by an alkyl group, by a phenyl, phenylmethyl, naphthyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl group, while the substituents may be identical or different, and

while an olefinic double bond of one of the abovementioned unsaturated heterocycles may be fused to a phenyl, naphthyl, pyridine, diazine, 1,3-oxazole, thienyl, furan, thiazole, pyrrole, *N*-methylpyrrole or quinoline ring, to a 1*H*-quinolin-2-one ring optionally substituted at the nitrogen atom by an alkyl group or to an imidazole or *N*-methylimidazole ring or also two olefinic double bonds of one of the abovementioned unsaturated heterocycles may each be fused to a phenyl ring,

while the phenyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl,

imidazolyl or 1-methylimidazolyl groups contained in R^1 as well as benzo-, thieno-, pyrido- and diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine, bromine or iodine atoms, by alkyl, alkoxy, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl, difluoromethyl, trifluoromethyl, alkoxycarbonyl, carboxy, hydroxy, amino, alkylamino, dialkylamino, acetyl, acetylamino, propionylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, alkanoyl, cyano, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, while the substituents may be identical or different,

R^2 denotes the hydrogen atom,

a phenylmethyl group or a C_{2-7}-alkyl group which may be substituted in the ω position by a cyclohexyl, phenyl, pyridinyl, diazinyl, hydroxy, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-(1-piperidinyl)-1-piperidinyl, 4-morpholinyl, hexahydro-1*H*-1-azepinyl, [bis-(2-hydroxyethyl)]amino, 4-alkyl-1-piperazinyl or 4-(ω-hydroxy-C_{2-7}-alkyl)-1-piperazinyl group,

a phenyl or pyridinyl group,

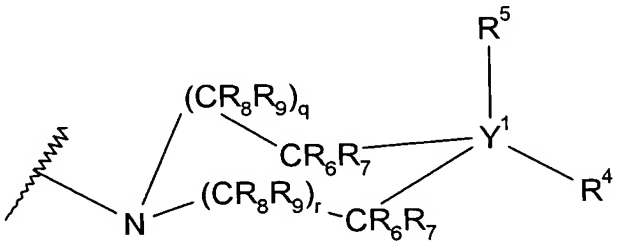
while the abovementioned heterocyclic groups and phenyl groups may additionally be mono- di- or trisubstituted in the carbon skeleton by fluorine, chlorine, bromine or iodine atoms, by methyl, alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, aminocarbonyl, cyano, methylsulphonyloxy, difluoromethoxy, trifluoromethoxy, trifluoromethylthio,

trifluoromethylsulphinyl, trifluoromethylsulphonyl, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl groups and the substituents may be identical or different,

R^3 denotes the hydrogen atom or a C_{1-3}-alkyl group optionally substituted by a phenyl or pyridinyl group,

while the C_{1-3}-alkyl group may be linked to an alkyl group present in R^2 or a phenyl or pyridyl ring present in R^2 , forming a ring, or

R^2 and R^3 together with the enclosed nitrogen atom denote a group of general formula



, (II)

wherein

Y^1 denotes the carbon atom or, if R^5 is a pair of free electrons, it may also denote the nitrogen atom,

q and r, if Y^1 denotes the carbon atom, represent the numbers 0, 1 or 2, or

q and r, if Y^1 denotes the nitrogen atom, represent the numbers 1 or 2,

R^4 denotes the hydrogen atom, an amino, alkylamino, dialkylamino, alkyl, cycloalkyl, amino-C_{2-7}-alkyl, alkylamino-C_{2-7}-alkyl, dialkylamino-C_{2-7}-alkyl, aminoiminomethyl, aminocarbonylamino, alkylaminocarbonylamino, cycloalkylaminocarbonylamino, phenylaminocarbonylamino,

aminocarbonylalkyl, aminocarbonylaminoalkyl, alkoxycarbonyl, alkoxycarbonylalkyl or carboxyalkyl group,

or, if Y^1 does not denote the nitrogen atom, the carboxy, aminomethyl, alkylaminomethyl or dialkylaminomethyl group,

a phenyl, pyridinyl, diazinyl, 1-naphthyl, 2-naphthyl, pyridinylcarbonyl or phenylcarbonyl group which may each be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine, bromine or iodine atoms, by alkyl, alkoxy, methylsulphonyloxy, difluoromethyl, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω -(dialkylamino)alkyl, ω-(dialkylamino)hydroxyalkyl, ω-(carboxy)alkanoyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, while the substituents may be identical or different,

a 4- to 10-membered azacycloalkyl group, a 6- to 10-membered oxaza, thiaza or diazacycloalkyl group, a 6- to 10-membered azabicycloalkyl group, a 1-alkyl-4-piperidinylcarbonyl or 4-alkyl-1-piperazinylcarbonyl group,

while the abovementioned mono- and bicyclic heterocycles are bound via a nitrogen or carbon atom,

in the abovementioned mono- and bicyclic heterocycles any methylene group not directly bound to a nitrogen, oxygen or sulphur atom may be substituted by one or two fluorine atoms,

the abovementioned mono- and bicyclic heterocycles as well as the 1-alkyl-4-piperidinylcarbonyl- and 4-alkyl-1-piperazinylcarbonyl group in the ring may be mono- or polysubstituted by a C_{1-7}-alkyl group,

monosubstituted by an alkanoyl, dialkylamino, phenylcarbonyl, pyridinylcarbonyl, carboxy, carboxyalkanoyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, aminocarbonyl, alkylamino-carbonyl, alkylsulphonyl, cycloalkyl or cycloalkylalkyl group, or substituted by a cycloalkylcarbonyl, azacycloalkylcarbonyl, diazacycloalkylcarbonyl or oxazacycloalkylcarbonyl group optionally alkyl-substituted in the ring,

while the alicyclic moieties contained in these substituents each comprise 3 to 10 ring members and the heteroalicyclic moieties each comprise 4 to 10 ring members and

the phenyl and pyridinyl groups contained in the abovementioned groups may in turn be mono-, di- or trisubstituted by fluorine, chlorine, bromine or iodine atoms, by alkyl, alkoxy, methylsulphonyloxy, difluoromethyl, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(carboxy)alkanoyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, while the substituents may be identical or different,

R^5 denotes a hydrogen atom,

a C_{1-4}-alkyl group , while an unbranched alkyl group may be substituted in the ω position by a phenyl, pyridinyl, diazinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl or hexahydro-1*H*-1-azepinyl group,

an alkoxycarbonyl, the cyano or aminocarbonyl group or also, if Y^1 denotes a nitrogen atom, a pair of free electrons,

or, if Y^1 does not denote a nitrogen atom, also the fluorine atom, or

R^4 together with R^5 and Y^1 denote a 4- to 7-membered cycloaliphatic ring, in which a methylene group may be replaced by a -NH or -N(alkyl)- group

while a hydrogen atom bound to a nitrogen atom within the group R^4 may be replaced by a protecting group,

R^6 and R^7, which may be identical or different, in each case denote a hydrogen atom, a C_{1-3}-alkyl group or also, if Y^1 does not denote a nitrogen atom, the fluorine atom and

R^8 and R^9, which may be identical or different, denote a hydrogen atom or a C_{1-3}-alkyl group,

while, unless otherwise stated, all the abovementioned alkyl and alkoxy groups as well as the alkyl groups present within the other groups specified comprise 1 to 7 carbon atoms and may be straight-chain or branched,

all the abovementioned cycloalkyl groups as well as the cycloalkyl groups present within the other groups specified, unless otherwise stated, may comprise 3 to 10 carbon atoms,

all the abovementioned aromatic and heteroaromatic groups may additionally be mono- di- or trisubstituted by fluorine, chlorine or bromine atoms, by cyano or hydroxy groups and the substituents may be identical or different and

by the protective groups mentioned in the foregoing and subsequent definitions are meant the protective groups familiar from peptide chemistry, particularly

a phenylalkoxycarbonyl group with 1 to 3 carbon atoms in the alkoxy moiety optionally substituted in the phenyl nucleus by a halogen atom, by a nitro or

phenyl group or by one or two methoxy groups,

for example the benzyloxycarbonyl, 2-nitro-benzyloxycarbonyl, 4-nitro-benzyloxycarbonyl, 4-methoxy-benzyloxycarbonyl, 2-chloro-benzyloxycarbonyl, 3-chloro-benzyloxycarbonyl, 4-chloro-benzyloxycarbonyl, 4-biphenylyl-α,α-dimethyl-benzyloxycarbonyl or 3,5-dimethoxy-α,α-dimethyl-benzyloxycarbonyl group,

an alkoxycarbonyl group with a total of 1 to 5 carbon atoms in the alkyl moiety,

for example the methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, 1-methylpropoxycarbonyl, 2-methylpropoxy-carbonyl or *tert*.butyloxycarbonyl group,

the allyloxycarbonyl, 2,2,2-trichloro-(1,1-dimethylethoxy)carbonyl or 9-fluorenylmethoxycarbonyl group or

the formyl, acetyl or trifluoroacetyl group.

A second embodiment of the present invention comprises the compounds of the above general formula (I), wherein

A, U, V, W, X, R^2 and R^3 are defined as mentioned in the first embodiment hereinbefore and

R^1 denotes a mono- or diunsaturated 5- to 7-membered aza, diaza, triaza or thiaza heterocyclic group,

in which the abovementioned heterocycles are linked via a carbon or nitrogen atom,

contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at a carbon atom by a phenyl, pyridinyl, diazinyl, thienyl, pyrrolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl or 1-methylpyrazolyl group and

an olefinic double bond of one of the abovementioned unsaturated heterocycles may be fused to a phenyl, naphthyl, pyridine, diazine, thienyl or quinoline ring or to a 1*H*-quinolin-2-one ring optionally substituted at the nitrogen atom by a methyl group,

while the phenyl, pyridinyl, diazinyl, thienyl, pyrrolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl or 1-methylpyrazolyl groups contained in R^1 as well as the benzo-, pyrido- and diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine, bromine or iodine atoms, by alkyl, alkoxy, nitro, difluoromethyl, trifluoromethyl, hydroxy, amino, alkylamino, dialkylamino, acetylamino, acetyl, cyano, difluoromethoxy or trifluoromethoxy groups, while the substituents may be identical or different,

while the abovementioned alkyl groups or the alkyl groups contained in the abovementioned groups, unless otherwise stated, contain 1 to 7 carbon atoms and may be branched or unbranched and the abovementioned aromatic and heteroaromatic groups may additionally be mono- di- or trisubstituted by fluorine, chlorine or bromine atoms or by cyano or hydroxy groups and the substituents may be identical or different.

A preferred second embodiment of the present invention comprises the compounds of the above general formula (I), wherein

A, U, V, W, X, R^2 and R^3 are as hereinbefore defined and

R^1 denotes a monounsaturated 5- to 7-membered diaza or triaza heterocyclic group,

while the abovementioned heterocycles are linked via a nitrogen atom,

contain a carbonyl group adjacent to a nitrogen atom and

may additionally be substituted at a carbon atom by a phenyl group,

and while an olefinic double bond of one of the abovementioned unsaturated heterocycles may be fused to a phenyl, thienyl or quinoline ring or to a 1*H*-quinolin-2-one ring optionally substituted at the nitrogen atom by a methyl group,

while the phenyl groups contained in R^1 as well as benzo-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine, bromine or iodine atoms, by methyl, methoxy, nitro, difluoromethyl, trifluoromethyl, hydroxy, amino, alkylamino, dialkylamino, acetylamino, acetyl, cyano, difluoromethoxy or trifluoromethoxy groups, while the substituents may be identical or different, but are preferably unsubstituted, or monosubstituted by a fluorine, chlorine or bromine atom or by a methyl or methoxy group,

while, unless otherwise stated, all the abovementioned alkyl groups as well as the alkyl groups present within the other groups comprise 1 to 7 carbon atoms and may be straight-chain or branched and the abovementioned aromatic and heteroaromatic groups may additionally be mono- di- or trisubstituted by fluorine, chlorine or bromine atoms or by cyano or hydroxy groups and the substituents may be identical or different.

A particularly preferred second embodiment of the present invention comprises the compounds of the above general formula (I), wherein

A, U, V, W, X, R^2 and R^3 are as hereinbefore defined and

R^1 denotes a 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-

yl, 4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl, 4-(5-oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)-piperidin-1-yl, 4-(2-oxo-1,2-dihydro-imidazo[4,5-c]quinolin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,2-dihydro-4*H*-thieno[3,4-d]pyrimidin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,4-dihydro-2*H*-thieno[3,2-d]pyrimidin-3-yl)-piperidin-1-yl, 4-(5-oxo-4,5,7,8-tetrahydro-2-thia-4,6-diaza-azulen-6-yl)-piperidin-1-yl, 4-(2-oxo-1,2,4,5-tetrahydro-thieno[3,2-d]-1,3-diazepin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,2,4,5-tetrahydro-thieno[2,3-d]-1,3-diazepin-3-yl)-piperidin-1-yl or 4-(2-oxo-1,4-dihydro-2*H*-thieno[2,3-d]pyrimidin-3-yl)-piperidin-1-yl group,

while the abovementioned mono- and bicyclic heterocycles in the carbon skeleton may additionally be monosubstituted by a methoxy group,

while the abovementioned aromatic and heteroaromatic groups by fluorine, chlorine or bromine atoms, by cyano or hydroxy groups may additionally be mono- di- or trisubstituted and the substituents may be identical or different.

A third embodiment of the present invention comprises the compounds of the above general formula (I), wherein

A, U, V, W, X and R^1 are as hereinbefore defined and

R^2 denotes the hydrogen atom or

a phenylmethyl group or a C_{2-7}-alkyl group which may be substituted in the ω position by a phenyl, pyridinyl, hydroxy, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, [bis-(2-hydroxyethyl)]amino group

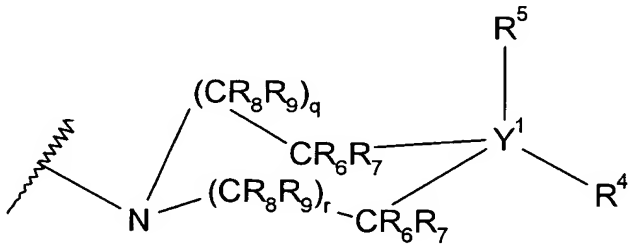
while the abovementioned heterocyclic groups and phenyl groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine, bromine or iodine atoms, by methyl, alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C_{1-3}-alkylamino, di-

(C_{1-3}-alkyl)-amino, acetylamino, aminocarbonyl, cyano, difluoromethoxy, trifluoromethoxy, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl groups and the substituents may be identical or different,

R^3 denotes the hydrogen atom or a C_{1-3}-alkyl group,

while the C_{1-3}-alkyl group may be linked to an alkyl group present in R^2 or a phenyl or pyridyl ring present in R^2, forming a ring, or

R^2 and R^3 together with the enclosed nitrogen atom denote a group of general formula



, (II)

wherein

Y^1 denotes the carbon atom or, if R^5 denotes a pair of free electrons, it may also denote the nitrogen atom,

q and r represent the numbers 1 or 2,

R^4 denotes the hydrogen atom, an amino, alkylamino or dialkylamino group,

a phenyl, pyridinyl or diazinyl group which may be substituted in each case by a fluorine, chlorine or bromine atom or by a methyl or methoxy group,

a 5- to 7-membered azacycloalkyl group, a 6- to 7-membered oxaza or diazacycloalkyl group or a 7- to 9-membered azabicycloalkyl group,

while the abovementioned mono- and bicyclic heterocycles are bound via a nitrogen or carbon atom,

in the abovementioned mono- and bicyclic heterocycles any methylene group not directly bound to a nitrogen, oxygen or sulphur atom may be substituted by one or two fluorine atoms,

the abovementioned mono- and bicyclic heterocycles may be substituted by a C_{1-3}-alkyl group, by a C_{1-4}-alkanoyl, di-(C_{1-3}-alkyl)-amino or C_{1-3}-alkylsulphonyl, by an alkoxycarbonyl, alkoxycarbonylalkyl, carboxy or carboxyalkyl group,

R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group or,

if Y^1 denotes a nitrogen atom, it may also denote a pair of free electrons,

R^6 and R^7, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group and

R^8 and R^9, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group,

while, unless otherwise stated, all the abovementioned alkyl groups as well as the alkyl groups present within the other groups comprise 1 to 7 carbon atoms and may be straight-chain or branched and the abovementioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by cyano or hydroxy groups and the substituents may be identical or different.

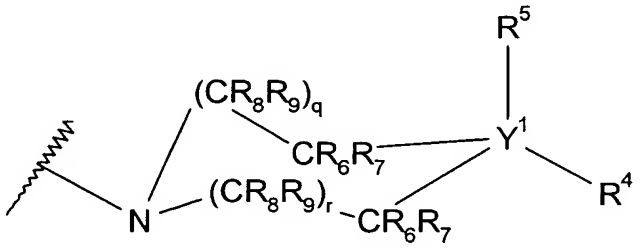
A preferred third embodiment of the present invention comprises the compounds of the above general formula (I), wherein

A, U, V, W, X and R^1 are as hereinbefore defined and

R^2 denotes a phenylmethyl group or a C_{2-7}-alkyl group which may be substituted in the ω position by a phenyl, amino, alkylamino or dialkylamino group,

while the abovementioned phenyl group may be substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl group, or

R^2 and R^3 together with the enclosed nitrogen atom denote a group of general formula



, (II)

wherein

Y^1 denotes the carbon atom or, if R^5 denotes a pair of free electrons, it may also denote the nitrogen atom,

q and r represent the number 1,

R^4 denotes the hydrogen atom,

a phenyl or pyridinyl group which may be substituted in each case by a fluorine, chlorine or bromine atom, by a methyl or methoxy group,

a dimethylamino, perhydro-azepin-1-yl, 4-methyl-perhydro-1,4-diazepin-1-yl, 1-methyl-1-piperidinyl-4-yl, 4-piperazin-1-yl, 4-acetyl-piperazin-1-yl, 4-cyclopropylmethyl-piperazin-1-yl, pyrrolidin-1-yl, 4-ethyl-piperazin-1-yl, 4-isopropyl-piperazin-1-yl, piperidin-1-yl, 4-morpholin-4-yl, 4,4-difluoro-1-piperidin-1-yl, 1-methyl-1-aza-bicyclo[3.2.1]oct-4-yl or 4-methyl-piperazin-1-yl group,

R^5 denotes a hydrogen atom or, if Y^1 denotes a nitrogen atom, it may also denote a pair of free electrons,

R^6 and R^7 in each case denote a hydrogen atom and

R^8 and R^9 in each case denote the hydrogen atom,

while, unless otherwise stated, all the abovementioned alkyl groups as well as the alkyl groups present within the other groups comprise 1 to 7 carbon atoms and may be straight-chain or branched and the abovementioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by cyano or hydroxy groups and the substituents may be identical or different,

while in all the embodiments mentioned above those compounds wherein

(i) A denotes an oxygen atom, a cyanoimino or phenylsulphonylimino group,

X denotes an oxygen atom, an imino or methylene group,

U denotes an unbranched C_{1-6}-alkyl group wherein each methylene group may be substituted by up to 2 fluorine atoms and the methyl group may be substituted by up to 3 fluorine atoms,

V denotes an amino or hydroxy group and

W denotes a hydrogen, chlorine or bromine atom or a trifluoromethyl group,

are of exceptional importance,

those compounds wherein

(ii) A denotes an oxygen atom,

X denotes an oxygen atom, an imino or methylene group,

U denotes a methyl or ethyl group wherein the methylene group may be substituted by up to 2 fluorine atoms and the methyl group may be substituted by up to 3 fluorine atoms,

V denotes an amino or hydroxy group and

W denotes a hydrogen, chlorine or bromine atom or a trifluoromethyl group,

are of particularly outstanding importance and

those compounds wherein

(iii) A denotes an oxygen atom,

X denotes an oxygen atom, an imino or methylene group,

U denotes a trifluoromethyl or pentafluoroethyl group,

V denotes an amino or hydroxy group and

W denotes a hydrogen, chlorine or bromine atom or a trifluoromethyl

group,

are of most particularly outstanding importance.

A fourth embodiment of the present invention comprises the compounds of the above general formula (I) wherein

A denotes an oxygen atom, a cyanoimino or phenylsulphonylimino group,

X denotes an oxygen atom, an imino or methylene group,

U denotes an unbranched C_{1-6}-alkyl group wherein each methylene group may be substituted by up to 2 fluorine atoms and the methyl group may be substituted by up to 3 fluorine atoms,

V denotes an amino or hydroxy group,

W denotes a hydrogen, chlorine or bromine atom or a trifluoromethyl group,

R^1 denotes a monounsaturated 5- to 7-membered diaza or triaza heterocyclic group,

while the abovementioned heterocycles are linked via a nitrogen atom,

contain a carbonyl group adjacent to a nitrogen atom,

may additionally be substituted at a carbon atom by a phenyl group and

an olefinic double bond of one of the abovementioned unsaturated heterocycles may be fused to a phenyl, thienyl or quinoline ring or to a 1*H*-quinolin-2-one ring optionally substituted at the nitrogen atom by a methyl group,

while the phenyl groups contained in R^1 as well as benzo-fused

heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine, bromine or iodine atoms, by methyl, methoxy, nitro, difluoromethyl, trifluoromethyl, hydroxy, amino, alkylamino, dialkylamino, acetylamino, acetyl, cyano difluoromethoxy or trifluoromethoxy groups, while the substituents may be identical or different, but are preferably unsubstituted or are monosubstituted by a fluorine, chlorine or bromine atom or by a methyl or methoxy group,

R^2 denotes the hydrogen atom or

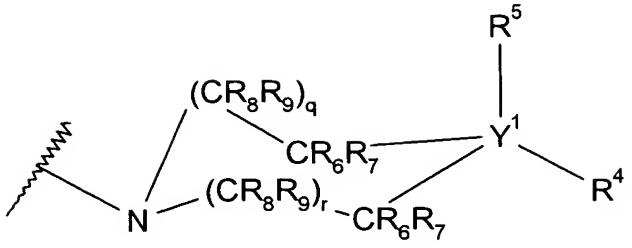
a phenylmethyl group or a C_{2-7}-alkyl group which may be substituted in the ω position by a phenyl, pyridinyl, hydroxy, amino, alkylamino, dialkylamino, alkoxycarbonyl, carboxy, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or [bis-(2-hydroxyethyl)]amino group,

while the abovementioned heterocyclic groups and phenyl groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine, bromine or iodine atoms, by methyl, alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, aminocarbonyl, cyano, difluoromethoxy, trifluoromethoxy, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl groups and the substituents may be identical or different,

R^3 denotes the hydrogen atom or a C_{1-3}-alkyl group,

while the C_{1-3}-alkyl group may be linked to an alkyl group present in R^2 or a phenyl or pyridyl ring present in R^2 , forming a ring, or

R^2 and R^3 together with the enclosed nitrogen atom denote a group of general formula



, (II)

wherein

Y^1 denotes the carbon atom or, if R^5 denotes a pair of free electrons, it may also denote the nitrogen atom,

q and r represent the numbers 1 or 2,

R^4 denotes the hydrogen atom, an amino, alkylamino or dialkylamino group,

a phenyl, pyridinyl or diazinyl group which may be substituted in each case by a fluorine, chlorine or bromine atom, by a methyl or methoxy group,

a 5- to 7-membered azacycloalkyl group, a 6- to 7-membered oxaza or diazacycloalkyl group or a 7- to 9-membered azabicycloalkyl group,

while the abovementioned mono- and bicyclic heterocycles are bound via a nitrogen or carbon atom,

in the abovementioned mono- and bicyclic heterocycles any methylene group not directly bound to a nitrogen, oxygen or sulphur atom may be substituted by one or two fluorine atoms,

the abovementioned mono- and bicyclic heterocycles may be substituted by a C_{1-3}-alkyl group, by a C_{1-4}-alkanoyl, di-(C_{1-3}-alkyl)-amino or C_{1-3}-alkylsulphonyl, by an alkoxycarbonyl,

alkoxycarbonylalkyl, carboxy or carboxyalkyl group,

R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group or,

if Y^1 denotes a nitrogen atom, it may also denote a pair of free electrons,

R^6 and R^7, which may be identical or different, in each case denote the hydrogen atom or a C_{1-3}-alkyl group and

R^8 and R^9, which may be identical or different, in each case denote the hydrogen atom or a C_{1-3}-alkyl group,

while, unless otherwise stated, the abovementioned alkyl groups or the alkyl groups contained in the abovementioned groups contain 1 to 7 carbon atoms and may be branched or unbranched and the abovementioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by cyano or hydroxy groups and the substituents may be identical or different.

A preferred fourth embodiment of the present invention comprises the compounds of the above general formula (I), wherein

A denotes an oxygen atom,

X denotes an oxygen atom, an imino or methylene group,

U denotes a methyl or ethyl group wherein the methylene group may be substituted by up to 2 fluorine atoms and the methyl group may be substituted by up to 3 fluorine atoms,

V denotes an amino or hydroxy group,

W denotes a hydrogen, chlorine or bromine atom or a trifluoromethyl group,

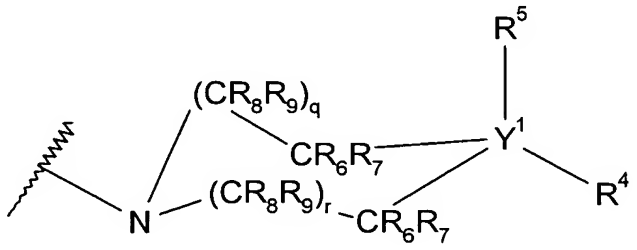
R^1 denotes a 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl, 4-(5-oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)-piperidin-1-yl, 4-(2-oxo-1,2-dihydro-imidazo[4,5-c]quinolin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,2-dihydro-4*H*-thieno[3,4-d]pyrimidin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,4-dihydro-2*H*-thieno[3,2-d]pyrimidin-3-yl)-piperidin-1-yl, 4-(5-oxo-4,5,7,8-tetrahydro-2-thia-4,6-diaza-azulen-6-yl)-piperidin-1-yl, 4-(2-oxo-1,2,4,5-tetrahydro-thieno[3,2-d]-1,3-diazepin-3-yl)-piperidin-1-yl, 4-(2-oxo-1,2,4,5-tetrahydro-thieno[2,3-d]-1,3-diazepin-3-yl)-piperidin-1-yl or 4-(2-oxo-1,4-dihydro-2*H*-thieno[2,3-d]pyrimidin-3-yl)-piperidin-1-yl group,

while the abovementioned mono- and bicyclic heterocycles in the carbon skeleton may additionally be monosubstituted by a methoxy group,

R^2 denotes a phenylmethyl group or a C_{2-7}-alkyl group which may be substituted in the ω position by a phenyl, amino, alkylamino or dialkylamino group,

while the abovementioned phenyl group may be substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl group, or

R^2 and R^3 together with the enclosed nitrogen atom denote a group of general formula



, (III)

wherein

Y^1 represents the carbon atom or, if R^5 denotes a pair of free electrons, it may also denote the nitrogen atom,

q and r represent the number 1,

R^4 denotes the hydrogen atom,

a phenyl or pyridinyl group which may be substituted in each case by a fluorine, chlorine or bromine atom, by a methyl or methoxy group,

a dimethylamino, perhydro-azepin-1-yl, 4-methyl-perhydro-1,4-diazepin-1-yl, 1-methyl-1-piperidinyl-4-yl, 4-piperazin-1-yl, 4-acetyl-piperazin-1-yl, 4-cyclopropylmethyl-piperazin-1-yl, pyrrolidin-1-yl, 4-ethyl-piperazin-1-yl, 4-isopropyl-piperazin-1-yl, piperidin-1-yl, 4-morpholin-4-yl, 4,4-difluoro-1-piperidin-1-yl, 1-methyl-1-aza-bicyclo[3.2.1]oct-4-yl or 4-methyl-piperazin-1-yl group,

R^5 denotes a hydrogen atom or, if Y^1 denotes a nitrogen atom, it may also denote a pair of free electrons,

R^6 and R^7 in each case denote a hydrogen atom and

R^8 and R^9 in each case denote the hydrogen atom,

while, unless otherwise stated, all the abovementioned alkyl groups as well as the alkyl groups present within the other groups comprise 1 to 7 carbon atoms and may be straight-chain or branched and the abovementioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by cyano or hydroxy groups and the substituents may be identical or different.

The following are mentioned as examples of most particularly preferred compounds of the above general formula (I):

(1) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(2) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(1'-methyl-[4,4']bipiperidinyl-1-yl)-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(3) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(4) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(5) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-1-(4-pyridin-4-yl-piperazin-1-yl)-butan-1,4-dione,

(6) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(1-methyl-piperidin-4-ylamino)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(7) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carboxylic acid-[(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-1,4'-bipiperidinyl-1'-yl-2-oxo-ethyl]-amide,

(8) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carboxylic acid-[1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-1,4'-bipiperidinyl-1'-yl-2-oxo-ethyl]-amide,

(9) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(4-dimethylamino-piperidin-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-

piperidin-1-yl]-butan-1,4-dione,

(10) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-perhydro-azepin-1-yl-piperidin-1-yl)-butan-1,4-dione,

(11) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(12) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(1'-methyl-4,4'-bipiperidinyl-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(13) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-piperazin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(14) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-piperazin-1-yl-piperidin-1-yl)-butan-1,4-dione,

(15) (*S*)-1-[4-(4-acetyl-piperazin-1-yl)-piperidin-1-yl]-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(16) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(3-dimethylamino-piperidin-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(17) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(5-oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)-piperidin-1-yl]-butan-1,4-dione,

(18) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(19) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2-dihydro-imidazo[4,5-c]quinolin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(20) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-cyclopropylmethyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(21) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2-dihydro-4*H*-thieno[3,4-d]pyrimidin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(22) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-thieno[3,2-d]pyrimidin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(23) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-pyrrolidin-1-yl-piperidin-1-yl)-butan-1,4-dione,

(24) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(5-oxo-4,5,7,8-tetrahydro-2-thia-4,6-diaza-azulen-6-yl)-piperidin-1-yl]-butan-1,4-dione,

(25) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-thieno[3,2-d]-1,3-diazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(26) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-thieno[2,3-

d]-1,3-diazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(27) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-thieno[2,3-d]pyrimidin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(28) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-ethyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(29) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-isopropyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(30) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-1,4'-bipiperidinyl-1'-yl-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(31) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-pyridin-4-yl-piperazin-1-yl)-butan-1,4-dione,

(32) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(3,4,5,6-tetrahydro-2*H*-4,4'-bipyridinyl-1-yl)-butan-1,4-dione,

(33) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(4,4-difluoro-1,4'-bipiperidinyl-1'-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

(34) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(4-morpholine-4-yl-piperidin-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione,

the enantiomers, the diastereomers and the salts thereof.

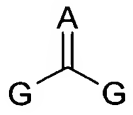
The compounds of general formula (I) are prepared by methods known in principle. The following methods have proved particularly satisfactory for preparing the compounds of general formula (I) according to the invention:

(a) In order to prepare compounds of general formula (I) wherein X denotes the NH group and R^1 to R^3 are as hereinbefore defined, with the proviso that these groups do not contain any free carboxylic acid function:

Reacting piperidines of general formula

, (III)

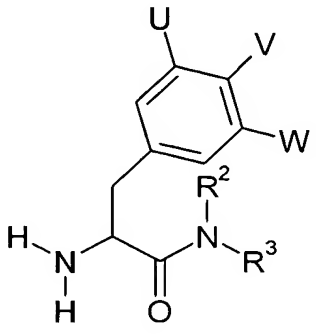
wherein R^1 is as hereinbefore defined, with carbonic acid derivatives of general formula



, (IV)

wherein A is as hereinbefore defined and G denotes a nucleofugic group, preferably the phenoxy, 1*H*-imidazol-1-yl, 1*H*-1,2,4-triazol-1-yl, trichloromethoxy or the 2,5-dioxopyrrolidin-1-yloxy group,

and with primary amines of general formula



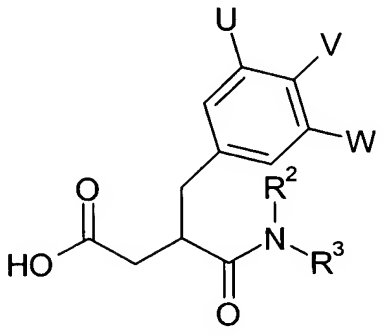
, (V)

wherein R^2 and R^3 are as hereinbefore defined, with the proviso that these groups do not contain any free carboxylic acid and/or any other free primary or secondary aliphatic amino function.

The fundamentally two-step reactions are normally carried out as one-pot processes, in which, preferably, in the first step, one of the two components (III) or (V) is reacted with equimolar amounts of the carbonic acid derivative of general formula (IV) in a suitable solvent at lower temperature, then at least equimolar amounts of the other component (III) or (V) are added and the reaction is completed at a higher temperature. The reactions with bis-(trichloromethyl)-carbonate are preferably carried out in the presence of at least 2 equivalents (based on bis-(trichloromethyl)-carbonate) of a tertiary base, for example triethylamine, *N*-ethyldiisopropylamine, pyridine, 1,5-diaza-bicyclo-[4,3,0]-non-5-ene, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo-[5,4,0]-undec-7-ene. The solvents used, which should be anhydrous, may be for example tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide, *N*-methyl-2-pyrrolidone, 1,3-dimethyl-2-imidazolidinone or acetonitrile, while if bis-(trichloromethyl)-carbonate is used as the carbonyl component anhydrous chlorohydrocarbons, for example dichloromethane, 1,2-dichloroethane or trichloroethylene are preferred. The reaction temperatures for the first reaction step are between –30°C and +25°C, preferably –5°C and +10°C, for the second reaction step between +15°C and the boiling temperature of the solvent used, preferably between +20°C and +70°C (cf. also: H. A. Staab and W. Rohr, "Synthesen mit heterocyclischen Amiden (Azoliden)", Neuere Methoden der Präparativen Organischen Chemie, Volume V, p. 53-93, Verlag Chemie, Weinheim/Bergstr., 1967; P. Majer and R.S. Randad, J. Org. Chem. 59, p. 1937-1938 (1994); K. Takeda, Y. Akagi, A. Saiki, T. Sukahara and H. Ogura, Tetrahedron Letters 24 (42), 4569-4572 (1983)).

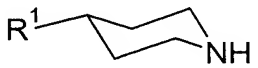
(b) In order to prepare compounds of general formula (I) wherein X denotes the methylene group and R^1 to R^3 are as hereinbefore defined, with the proviso that these groups do not contain any free carboxylic acid and/or other free primary or secondary aliphatic amino function:

Coupling a carboxylic acid of general formula



, (VI)

wherein U, V, W, R^2 and R^3 are as hereinbefore defined, to a piperidine of general formula



, (III)

wherein R^1 has the meanings given hereinbefore.

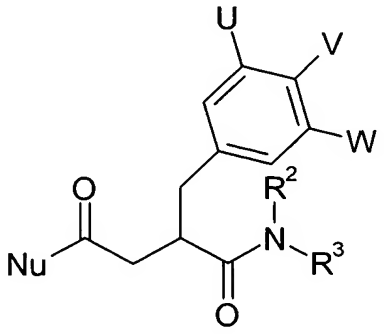
The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)- N,N-N',N'-tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexa-fluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling reagent in solvents such as dichloromethane, tetrahydrofuran, acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), N-methylpyrrolidone (NMP) or mixtures thereof and at temperatures between -30 and +30°C, preferably -20

and +25°C. If necessary, N-ethyl-diisopropylamine (DIEA) (Hünig base) is preferably used as an additional auxiliary base.

The so-called anhydride process is used as a further coupling method for synthesising compounds of general formula (I) (cf. also: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, p. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, p. 21-27). The Vaughan variant of the mixed anhydride process is preferred (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), in which the mixed anhydride of the carboxylic acid of general formula (VI) which is to be coupled and monoisobutyl carbonate is obtained, using isobutyl chlorocarbonate in the presence of bases such as 4-methyl-morpholine or 4-ethylmorpholine. The preparation of this mixed anhydride and the coupling with amines are carried out in a one-pot process, using the abovementioned solvents and at temperatures between -20 and +25°C, preferably 0°C and +25°C.

(c) In order to prepare compounds of general formula (I) wherein X denotes the methylene group and R^2 and R^3 are as hereinbefore defined, with the proviso that these groups do not contain any free primary or secondary amine:

Coupling a compound of general formula



, (VII)

wherein U, V, W, R^2 and R^3 are as hereinbefore defined, with the proviso that R^2 and R^3 do not contain any free primary or secondary amine, and Nu denotes a leaving group, for example a halogen atom, such as the chlorine,

bromine or iodine atom, an alkylsulphonyloxy group with 1 to 10 carbon atoms in the alkyl moiety, a phenylsulphonyloxy or naphthylsulphonyloxy group optionally mono-, di- or trisubstituted by chlorine or bromine atoms or by methyl or nitro groups, while the substituents may be identical or different, a 1*H*-imidazol-1-yl, a 1*H*-pyrazol-1-yl optionally substituted by one or two methyl groups in the carbon skeleton, a 1*H*-1,2,4-triazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3,4-tetrazol-1-yl, a vinyl, propargyl, *p*-nitrophenyl, 2,4-dinitrophenyl, trichlorophenyl, pentachlorophenyl, pentafluorophenyl, pyranyl or pyridinyl, a dimethylaminyloxy, 2(1*H*)-oxopyridin-1-yl-oxy, 2,5-dioxopyrrolidin-1-yloxy, phthalimidyloxy, 1*H*-benzo-triazol-1-yloxy or azide group,

with a piperidine of general formula

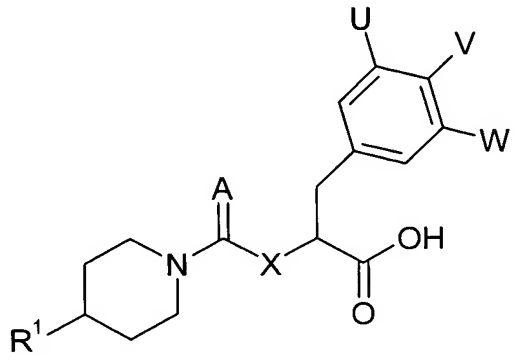
, (III)

wherein R^1 is as hereinbefore defined.

The reaction is carried out under Schotten-Baumann or Einhorn conditions, i.e. the components are reacted in the presence of at least one equivalent of an auxiliary base at temperatures between -50°C and +120°C, preferably -10°C and +30°C, and optionally in the presence of solvents. The auxiliary bases used are preferably alkali metal and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal carbonates, e.g. sodium carbonate, potassium carbonate or caesium carbonate, alkali metal acetates, e.g. sodium or potassium acetate, as well as tertiary amines, e.g. pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyl-diisopropylamine, N-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, the solvents used may be, for example, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methyl-pyrrolidone or mixtures thereof; if alkali metal or alkaline earth metal hydroxides, alkali metal carbonates or acetates are used as the auxiliary bases, water may also be added to the reaction mixture as cosolvent.

(d) In order to prepare compounds of general formula (I) wherein all the groups are as hereinbefore defined:

Coupling a carboxylic acid of general formula



, (VIII)

wherein all the groups are as hereinbefore defined, with an amine of general formula HNR^2R^3, wherein R^2 and R^3 are as hereinbefore defined, with the proviso that it does not contain any free carboxylic acid and/or other free primary or secondary aliphatic amino function.

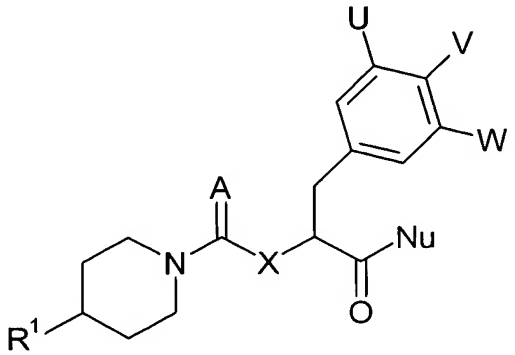
The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)- N,N-N',N'-tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexa-fluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling reagent in solvents such as dichloromethane, tetrahydrofuran, acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), N-methylpyrrolidone (NMP) or mixtures thereof and at temperatures between -30 and +30°C, preferably -20

and +25°C. If necessary, N-ethyl-diisopropylamine (DIEA) (Hünig base) is preferably used as an additional auxiliary base.

The so-called anhydride process is used as a further coupling method for synthesising compounds of general formula (I) (cf. also: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, p. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, p. 21-27). The Vaughan variant of the mixed anhydride process is preferred (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), in which the mixed anhydride of the carboxylic acid of general formula (VI) which is to be coupled and monoisobutyl carbonate is obtained, using isobutyl chlorocarbonate in the presence of bases such as 4-methyl-morpholine or 4-ethylmorpholine. The preparation of this mixed anhydride and the coupling with amines are carried out in a one-pot process, using the abovementioned solvents and at temperatures between -20 and +25°C, preferably 0°C and +25°C.

(e) In order to prepare compounds of general formula (I) wherein R^1 is as hereinbefore defined, with the proviso that no free primary or secondary amine is present:

Coupling a compound of general formula



, (IX)

wherein all the groups are as hereinbefore defined and Nu denotes a leaving group, for example a halogen atom, such as the chlorine, bromine or iodine atom, an alkylsulphonyloxy group with 1 to 10 carbon atoms in the alkyl

moiety, a phenylsulphonyloxy or naphthylsulphonyloxy group optionally mono-, di- or trisubstituted by chlorine or bromine atoms, by methyl or nitro groups, while the substituents may be identical or different, a 1*H*-imidazol-1-yl, a 1*H*-pyrazol-1-yl optionally substituted by one or two methyl groups in the carbon skeleton, a 1*H*-1,2,4-triazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3,4-tetrazol-1-yl, a vinyl, propargyl, *p*-nitrophenyl, 2,4-dinitrophenyl, trichlorophenyl, pentachlorophenyl, pentafluorophenyl, pyranyl or pyridinyl, a dimethylaminyloxy, 2(1*H*)-oxopyridin-1-yl-oxy, 2,5-dioxopyrrolidin-1-yloxy, phthalimidyloxy, 1*H*-benzo-triazol-1-yloxy or azide group,

with an amine of general formula HNR^2R^3, wherein R^2 and R^3 are as hereinbefore defined, with the proviso that no free carboxylic acid and/or other free primary or secondary aliphatic amino function is present.

The reaction is carried out under Schotten-Baumann or Einhorn conditions, i.e. the components are reacted in the presence of at least one equivalent of an auxiliary base at temperatures between -50°C and +120°C, preferably -10°C and +30°C, and optionally in the presence of solvents. The auxiliary bases used are preferably alkali metal and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal carbonates, e.g. sodium carbonate, potassium carbonate or caesium carbonate, alkali metal acetates, e.g. sodium or potassium acetate, as well as tertiary amines, e.g. pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyl-diisopropylamine, N-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, the solvents used may be, for example, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methyl-pyrrolidone or mixtures thereof; if alkali metal or alkaline earth metal hydroxides, alkali metal carbonates or acetates are used as the auxiliary bases, water may also be added to the reaction mixture as cosolvent.

The new compounds of general formula (I) according to the invention contain one or more chiral centres. If for example there are two chiral centres the compounds may occur in the form of two pairs of diastereomeric antipodes.

The invention covers the individual isomers as well as the mixtures thereof.

The diastereomers may be separated on the basis of their different physico-chemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

Racemates covered by general formula (I) may be separated for example by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+)-camphorsulphonic acid, or an optically active base, for example with (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound of general formula (I) is reacted with one of the abovementioned optically active acids or bases in equimolar amounts in a solvent and the resulting crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvent provided that it is sufficiently different in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. dilute hydrochloric acid or aqueous methanesulphonic acid, and in this way the corresponding free compound is obtained in the (+) or (-) form.

The (R) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds covered by general formula I may also be obtained by performing the syntheses described above with a suitable reaction component in the (R) or (S) configuration.

The starting compounds of general formula (III) may be obtained, if they are not known from the literature or even commercially available, according to the processes described in WO 98/11128 and DE 199 52 146. The starting compounds of general formula (IV) are commercially available. Compounds of general formula (V) may be obtained by methods familiar to the peptide chemist from protected phenylalanines and amines of general formula HNR^2R^3. The starting compounds of general formula (VI) are obtained for example by reacting amines of general formula HNR^2R^3 with 2-(alkoxycarbonylmethyl)-3-aryl-propanoic acids and subsequently hydrolytically cleaving the alkyl group. The 2-(alkoxycarbonylmethyl)-3-aryl-propanoic acids required may be prepared analogously to methods known from the literature (David A. Evans, Leester D. Wu, John J. M. Wiener, Jeffrey S. Johnson, David H. B. Ripin and Jason S. Tedrow, J. Org.Chem 64, 6411-6417 [1999]; Saul G. Cohen and Aleksander Milovanovic, J. Am. Chem. Soc. 90, 3495-3502 [1968]; Hiroyuki Kawano, Youichi Ishii, Takao Ikariya, Masahiko Saburi, Sadao Yoshikawa, Yasuzo Uchida and Hidenori Kumobayashi, Tetrahedron Letters 28, 1905-1908 [1987]). Carboxylic acids of general formula (VIII) may be prepared from generally available starting materials in accordance with the processes described in WO 98/11128.

The compounds of general formula I obtained may, if they contain suitable basic functions, be converted, particularly for pharmaceutical use, into their physiologically acceptable salts with inorganic or organic acids. Suitable acids include for example hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid.

Moreover, the new compounds of formula (I), if they contain a carboxylic acid function, may if desired be converted into the addition salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable addition salts thereof. Suitable bases for this include, for example, sodium hydroxide, potassium hydroxide, ammonia,

cyclohexylamine, dicyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The present invention relates to racemates if the compounds of general formula (I) have only one chiral element. However, the application also includes the individual diastereomeric pairs of antipodes or mixtures thereof which are obtained if there is more than one chiral element in the compounds of general formula (I), as well as the individual optically active enantiomers of which the abovementioned racemates are made up.

The new compounds of general formula (I) and the physiologically acceptable salts thereof have valuable pharmacological properties, based on their selective CGRP-antagonistic properties. The invention further relates to pharmaceutical compositions containing these compounds, their use and the preparation thereof.

The new compounds of general formula I and the physiologically acceptable salts thereof have CGRP-antagonistic properties and exhibit good affinities in CGRP receptor binding studies. The compounds display CGRP-antagonistic properties in the pharmacological test systems described hereinafter.

The following experiments were carried out to demonstrate the affinity of the abovementioned compounds for human CGRP-receptors and their antagonistic properties:

A. Binding studies with SK-N-MC cells (expressing the human CGRP receptor)

SK-N-MC cells are cultivated in "Dulbecco's modified Eagle medium". The medium is removed from confluent cultures. The cells are washed twice with PBS buffer (Gibco 041-04190 M), detached by the addition of PBS buffer mixed with 0.02% EDTA, and isolated by centrifuging. After resuspension in 20 ml of "Balanced Salts Solution" [BSS (in mM): NaCl 120, KCl 5.4, $NaHCO_3$ 16.2, $MgSO_4$ 0.8, $NaHPO_4$ 1.0, $CaCl_2$ 1.8, D-glucose 5.5, HEPES 30, pH 7.40] the cells are centrifuged twice at 100 x g and resuspended in BSS. After the number of cells has been determined, the cells are homogenised using an Ultra-Turrax and centrifuged for 10 minutes at 3000 x g. The supernatant is discarded and the pellet is recentrifuged in Tris buffer (10 mM Tris, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) enriched with 1% bovine serum albumin and 0.1% bacitracin, and resuspended (1 ml / 1000000 cells). The homogenised product is frozen at -80°C. The membrane preparations are stable for more than 6 weeks under these conditions.

After thawing, the homogenised product is diluted 1:10 with assay buffer (50 mM Tris, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) and homogenised for 30 seconds with an Ultra-Turrax. 230 µl of the homogenised product are incubated for 180 minutes at ambient temperature with 50 pM ^{125}I-iodotyrosyl-Calcitonin-Gene-Related Peptide (Amersham) and increasing concentrations of the test substances in a total volume of 250 µl. The incubation is ended by rapid filtration through GF/B-glass fibre filters treated with polyethyleneimine (0.1%) using a cell harvester. The protein-bound radioactivity is measured using a gamma counter. Non-specific binding is defined as the bound radioactivity in the presence of 1 µM human CGRP-alpha during incubation.

The concentration binding curves are analysed using computer-aided non-linear curve matching.

The compounds mentioned hereinbefore show IC_{50} values $\leq$ 10000 nM in the test described.

B. CGRP Antagonism in SK-N-MC cells

SK-N-MC cells (1 million cells) are washed twice with 250 µl incubation buffer (Hanks' HEPES, 1 mM 3-isobutyl-1-methylxanthine, 1% BSA, pH 7.4) and pre-incubated at 37°C for 15 minutes. After the addition of CGRP (10 µl) as agonist in increasing concentrations (10^{-11} to 10^{-6} M), or additionally the substance in 3 to 4 different concentrations, the mixture is incubated for another 15 minutes.

Intracellular cAMP is then extracted by the addition of 20 µl of 1M HCl and centrifugation (2000 x g, 4°C, for 15 minutes). The supernatants are frozen in liquid nitrogen and stored at -20°C.

The cAMP contents of the samples are determined by radioimmunoassay (Messrs. Amersham) and the pA_2 values of antagonistically acting substances are determined graphically.

The compounds of general formula I exhibit CGRP-antagonistic properties in the *in vitro* test model described, in a dosage range between 10^{-12} and 10^{-5} M.

In view of their pharmacological properties the compounds of general formula I and the salts thereof with physiologically acceptable acids are thus suitable for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches. Moreover, the compounds of general formula I also have a positive effect on the following diseases: non-insulin-dependent diabetes mellitus ("NIDDM"), cardiovascular diseases, morphine tolerance, diarrhoea caused by clostridium toxin, skin diseases, particularly thermal and radiation-induced skin damage including sunburn, inflammatory diseases, e.g. inflammatory diseases of the joints (arthritis), neurogenic inflammation of the oral mucosa, inflammatory lung diseases, allergic rhinitis, asthma, diseases

accompanied by excessive vasodilatation and resultant reduced blood supply to the tissues, e.g. shock and sepsis. In addition, the compounds according to the invention have a general pain-relieving effect. The symptoms of menopausal hot flushes caused by vasodilatation and increased blood flow in oestrogen-deficient women and hormone-treated patients with prostate carcinoma are favourably affected by the CGRP-antagonists of the present application in a preventive and acute-therapeutic capacity, this therapeutic approach being distinguished from hormone replacement by the absence of side effects.

The dosage required to achieve a corresponding effect is conveniently 0.0001 to 3 mg/kg of body weight, preferably 0.01 to 1 mg/kg of body weight, when administered intravenously or subcutaneously and 0.01 to 10 mg/kg of body weight, preferably 0.1 to 10 mg/kg of body weight when administered orally, nasally or by inhalation, 1 to 3 x a day in each case.

If the treatment with CGRP antagonists and/or CGRP release inhibitors is given as a supplement to conventional hormone substitution, it is advisable to reduce the doses specified above, in which case the dosage may be from 1/5 of the lower limits mentioned above up to 1/1 of the upper limits specified.

The compounds prepared according to the invention may be administered either on their own or optionally in combination with other active substances for the treatment of migraine by intravenous, subcutaneous, intramuscular, intrarectal, intranasal route, by inhalation, transdermally or orally, while aerosol formulations are particularly suitable for inhalation. The combinations may be administered either simultaneously or sequentially.

Categories of active substance which may be used in the combination include e.g. antiemetics, prokinetics, neuroleptics, antidepressants, neurokinine antagonists, anticonvulsants, histamine-H1 receptor antagonists, antimuscarinics, β-blockers, α-agonists and α-antagonists, ergot alkaloids, mild analgesics, non-steroidal antiinflammatories, corticosteroids, calcium

antagonists, 5-$HT_{1B/1D}$ agonists or other anti-migraine agents, which may be formulated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinyl pyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, metered dose aerosols or suppositories.

Thus other active substances which may be used for the combinations mentioned above include for example the non-steroidal antiinflammatories acclofenac, acemetacin, acetylsalicylic acid, azathioprine, diclofenac, diflunisal, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, leflunomide, lornoxicam, mefenamic acid, naproxen, phenylbutazone, piroxicam, sulphasalazine, zomepirac or the pharmaceutically acceptable salts thereof as well as meloxicam and other selective COX2-inhibitors, such as for example rofecoxib and celecoxib.

It is also possible to use ergotamine, dihydroergotamine, metoclopramide, domperidone, diphenhydramine, cyclizine, promethazine, chlorpromazine, vigabatrin, timolol, isometheptene, pizotifen, botox, gabapentin, topiramate, riboflavin, montelukast, lisinopril, prochloroperazine, dexamethasone, flunarizine, dextropropoxyphene, meperidine, metoprolol, propranolol, nadolol, atenolol, clonidine, indoramin, carbamazepine, phenytoin, valproate, amitryptiline, lidocaine or diltiazem and other 5-$HT_{1B/1D}$-agonists such as, for example, almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan.

The dosage of these active substances is expediently 1/5 of the lowest recommended dose to 1/1 of the normally recommended dose, i.e. for example 20 to 100 mg of sumatriptan.

The invention further relates to the use of the compounds according to the

invention as valuable adjuvants for the production and purification (by affinity chromatography) of antibodies as well as in RIA and ELISA assays, after suitable radioactive labelling, for example by tritiation of suitable precursors, for example by catalytic hydrogenation with tritium or replacing halogen atoms with tritium, and as a diagnostic or analytical adjuvant in neurotransmitter research.

Experimental section

As a rule, melting points, IR, UV, ^{1}H-NMR and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated, Rf values were obtained using ready-made silica gel TLC plates 60 F_{254} (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation. The R_f values obtained under the name Alox were obtained using ready-made aluminium oxide 60 F_{254} TLC plates (E. Merck, Darmstadt, item no. 1.05713) without chamber saturation. The ratios given for the eluants relate to units by volume of the solvent in question. For chromatographic purification, silica gel made by Millipore (MATREX^{TM}, 35-70 my) was used. If no detailed information is given as to the configuration, it is not clear whether it is a pure enantiomer or whether partial or even complete racemisation has occurred.

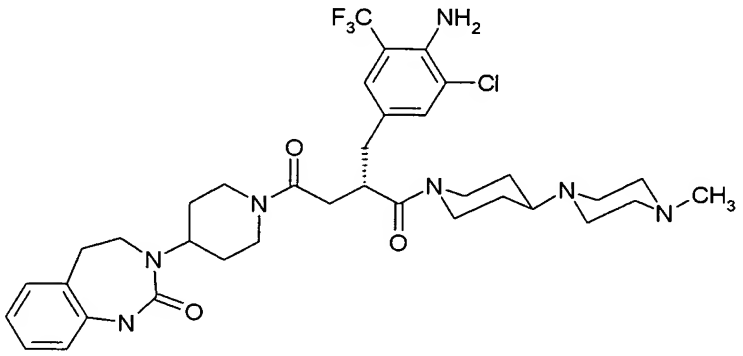
The following abbreviations are used in the description of the experiments:

abs.	absolute
Boc	*tert.*-butoxycarbonyl
CDI	*N,N'*-carbonyldiimidazole
CDT	1,1'-carbonyldi-(1,2,4-triazole)
DMF	*N,N*-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethanol
sat.	saturated
semiconc.	semiconcentrated
HCl	hydrochloric acid
HOAc	acetic acid

HOBt	1-hydroxybenzotriazole-hydrate
i. vac.	*in vacuo* (in a vacuum)
KOH	potassium hydroxide
conc.	concentrated
MeOH	methanol
MTBE	methyl-*tert.*-butylether
NaCl	sodium chloride
NaOH	sodium hydroxide
org.	organic
RT	room temperature
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Example 1

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



1a) (4-amino-3-chloro-5-trifluoromethyl-phenyl)-methanol

69.56 g (0.43 mol) CDI were added to a solution of 93.4 g (0.39 mol) 4-amino-3-chloro-5-trifluoromethyl-benzoic acid (described in *Arzneim.-Forsch.* **1984**, *34*(11A), 1612-1624) in 1 L THF and the mixture was stirred for 1 hour at 40°C. The reaction mixture was then carefully added to a solution of 51.4 g (1.36 mol) $NaBH_4$ in 450 mL of water at RT under a nitrogen atmosphere and with cooling. The mixture was stirred for 2 hours at RT, combined with 500 mL water and 300 mL semiconc. HCl, stirred for another hour and then exhaustively extracted with EtOAc. The combined org. phases were dried over Na_2SO_4 and evaporated down i. vac.. The oil remaining was combined with 500 mL petroleum ether and stirred while cooling with ice. The precipitate was suction filtered, washed with petroleum ether and dried. 29.7 g of the desired product were obtained.

The mother liquor was evaporated down again, combined with petroleum ether and cooled. The precipitate obtained was again washed with petroleum ether and dried. A further 21.8 g of the desired product were obtained.

Yield: 51.5 g (59% of theory) of a white solid

R_f = 0.73 (eluant: petroleum ether/EtOAc = 1/1)

1b) 4-amino-3-chloro-5-trifluoromethyl-benzaldehyde

A mixture of 17.0 g (75.4 mmol) of (4-amino-3-chloro-5-trifluoromethyl-phenyl)-methanol, 100 g (1.15 mol) of manganese dioxide and 300 mL of CH_2Cl_2 was stirred overnight at RT. The precipitate was suction filtered and the solution evaporated down i. vac.. The desired product was obtained as a white solid.

Yield: 16.0 g (95% of theory)
ESI-MS: $(M+H)^+$ = 224/226 (Cl)

1c) diethyl [2-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-phosphonate

A solution of 168.0 g (0.56 mol) (*R*)-4-benzyl-3-(2-bromo-acetyl)-oxazolidin-2-one and 188.6 mL (1.1 mol) of triethylphosphite was stirred for 1.5 hours at 60°C, while the ethylbromide formed was distilled off. The reaction mixture was concentrated by evaporation i. vac. and the residue remaining was purified by chromatography on silica gel. The desired product was obtained in the form of a yellowish-brown oil.

Yield: 130 g (65 % of theory)
ESI-MS: $(M+H)^+$ = 356

1d) (*R*)-3-[(*E*)-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-acryloyl]-4-benzyl-oxazolidin-2-one

Under a nitrogen atmosphere 3.93 g (90.0 mmol) of NaH (55% in mineral oil) were added batchwise to a solution of 31.98 g (90.0 mmol) of diethyl [2-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-phosphonate in 400 mL of THF. The reaction mixture was stirred for 30 minutes at RT and for a further 35 minutes at 35°C. After the development of gas had ended, 16.0 g (71.5 mmol)

of 4-amino-3-chloro-5-trifluoromethyl-benzaldehyde, dissolved in 50 mL THF, were added dropwise and stirred for a further 12 hours at RT. The reaction solution was combined with saturated aqueous NH_4Cl solution, the mixture was extracted exhaustively with EtOAc and the combined extracts were dried and evaporated down i. vac.. The residue remaining was purified by chromatography on silica gel. The desired product was obtained in the form of a yellow oil.

Yield: 38.2 g (62% of theory)
ESI-MS: $(M+H)^+$ = 425/427 (Cl)
R_f = 0.55 (eluant: petroleum ether/EtOAc = 2/1)

1e) (*R*)-3-[3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionyl]-4-benzyl-oxazolidin-2-one

A mixture of 23.7 g (55.8 mmol) of (*R*)-3-[(*E*)-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-acryloyl]-4-benzyl-oxazolidin-2-one, 400 mL of MeOH and 5.0 g of Raney nickel was shaken for 2 hours at RT and 3 bar of hydrogen pressure in a Parr autoclave. The catalyst was suction filtered and the solvent removed i. vac.. The desired product was obtained in the form of a yellow oil.

Yield: 22.5 g (95% of theory)
ESI-MS: $(M+H)^+$ = 427/429 (Cl)

1f) *tert*.-butyl (*S*)-3-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxo-butanoate

Under an argon atmosphere 63.24 mL (63.24 mmol) of a sodium-bis(trimethylsilyl)-amide solution (1 M in THF) was added dropwise to a solution of 22.5 g (52.71 mmol) of (*R*)-3-[3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionyl]-4-benzyl-oxazolidin-2-one in 105 mL THF which had been cooled to –78°C and the mixture was stirred for 2 hours at -78°C. 38.9 mL (263.5 mmol) of *tert*.butyl bromoacetate were added dropwise

to the reaction mixture at –78°C, this was stirred for a further 24 hours at -78°C and then heated to RT. After the addition of 200 mL of a saturated aqueous NH_4Cl solution the mixture was extracted twice with 300 mL of EtOAc, the combined org. phases were dried over Na_2SO_4 and evaporated down i. vac.. The residue remaining was purified by chromatography on silica gel. The desired product was obtained in the form of a yellow oil.

Yield: 15.6 g (55% of theory)
ESI-MS: $(M+H)^+$ = 541/543 (Cl)
R_f = 0.35 (eluant: petroleum ether/EtOAc = 8/2)

1g) 4-*tert*.-butyl (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-succinate

11.75 ml (115.1 mmol) 35% H_2O_2 was added to a solution of 2.51 g (57.6 mmol) lithium hydroxide hydrate in 150 mL of water. This mixture was then added dropwise to an ice-cooled solution of 15.6 g (28.8 mmol) of *tert*.-butyl (*S*)-3-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxo-butanoate in 600 mL of THF and the reaction mixture was stirred for a further 2 hours while cooling with ice. Then 150 mL of saturated aqueous sodium sulphite solution were added to the reaction mixture and acidified with aqueous citric acid solution. The org. phase was separated off, dried and evaporated down i. vac.. 15.6 g of a viscous yellow oil were obtained.
The aqueous phase was exhaustively extracted with EtOAc, the combined org. phases were washed with water, dried and evaporated down i. vac.. A further 5.5 g of a yellow oil were obtained.
The crude product, which still contained (*R*)-4-benzyl-oxazolidin-2-one, was further reacted without purification.

Yield: 21.1 g crude product
ESI-MS: $(M+H)^+$ = 380/382 (Cl)

1g) tert. butyl (*S*)-3-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-oxo-butanoate

A mixture of 15.4 g (40.3 mmol) of 4-tert. butyl (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-succinate, 7.4 g (40.3 mmol) of (1-methyl-4-piperidin-4-yl)-piperazine, 5.45 g (40.3 mmol) of HOBt, 12.94 g (40.3 mmol) of TBTU, 11.77 mL (85.0 mmol) of triethylamine and 400 mL of THF was stirred for 12 hours at RT. Then the mixture was evaporated down i. vac. and the residue remaining was distributed between EtOAc and aqueous $NaHCO_3$ solution. The org. phase was separated off, dried and evaporated down i. vac.. The residue obtained was purified by chromatography on aluminium oxide. The desired product was obtained in the form of a yellow oil.

Yield: 11.0 g (50% of theory)
ESI-MS: $(M+H)^+$ = 547/549 (Cl)
R_f = 0.35 (Alox; eluant: EtOAc/CH_2Cl_2 = 6/4)

1h) (*S*)-3-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-oxo-butanoic acid

5.75 g (38.4 mmol) of NaI, 3 mL of anisol and 4.92 mL (38.4 mmol) of trimethylsilylchloride were added to the solution of 7.0 g (12.8 mmol) of tert. butyl (*S*)-3-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-oxo-butanoate in 375 mL acetonitrile. The reaction mixture was stirred for 90 minutes at 40°C, combined with another 5.75 g (38.4 mmol) of NaI and 4.92 mL (38.4 mmol) of trimethylsilylchloride and stirred for a further 2 hours at 40°C. The mixture was evaporated down i. vac. and further reacted as the crude product.

1i) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione

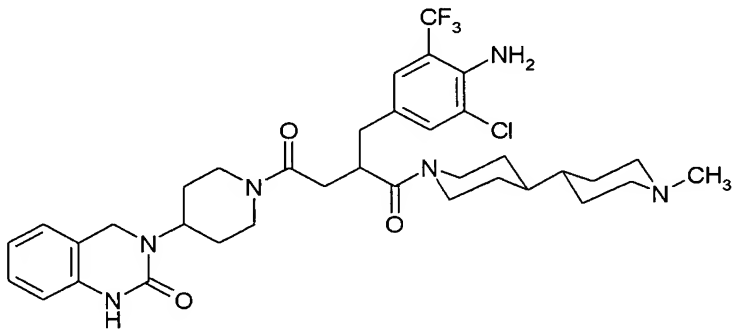
A mixture of 6.3 g (12.8 mmol) of (*S*)-3-(4-amino-3-chloro-5-trifluoromethyl-

benzyl)-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-oxo-butanoic acid, 3.16 g (12.9 mmol) of 3-piperidin-4-yl-1,3,4,5-tetrahydro-benzo[d][1,3]-diazepin-2-one, 4.66 g (14.5 mmol) of TBTU, 1.96 g (14.5 mmol) of HOBt, 9.45 mL (68 mmol) of triethylamine and 300 mL DMF was stirred for 12 hours at RT. The reaction mixture was evaporated down i. vac., the residue was distributed between EtOAc and saturated aqueous $NaHCO_3$ solution. The org. phase was separated off, dried and evaporated down i. vac.. The residue was purified by chromatography on silica gel. The yellow oil obtained was triturated with ether and suction filtered. The desired product was obtained in the form of a white solid.

Yield: 3.8 g (39% of theory)
ESI-MS: $(M+H)^+$ = 718/20 (Cl)
R_f = 0.22 (eluant: EtOAc/MeOH/conc. aqueous NH_3 = 70/30/3)

Example 2

2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(1'-methyl-[4,4']bipiperidinyl-1-yl)-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione



2a) 2-chloro-4-chloromethyl-6-trifluoromethyl-phenylamine

0.94 mL (13.00 mmol) of $SOCl_2$ was added at RT to a solution of 1.00 g (4.43 mmol) of (4-amino-3-chloro-5-trifluoromethyl-phenyl)-methanol in 50 mL CH_2Cl_2 and the mixture was stirred for 3 hours at RT. The reaction mixture was poured onto ice and the aqueous phase was exhaustively extracted with

CH_2Cl_2. The combined org. phases were washed with ice-cold $NaHCO_3$ solution, dried over Na_2SO_4, filtered through activated charcoal and evaporated down i. vac.. The crude product was used in the following reaction step without any further purification.

Yield: 1.08 g (quantitative yield)
EI-MS: M^+ = 243/245/247 (Cl_2)
R_f = 0.81 (eluant: petroleum ether/EtOAc = 2/1)

2b) tert.butyl 4-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-3,3-bis-ethoxycarbonyl-butyrate

193 mg (4.43 mmol) of NaH (55% in mineral oil) was added batchwise to a solution of 1.20 g (4.43 mmol) of 1-*tert*.-butyl-4-ethyl 3-ethoxycarbonyl-succinate in 50 mL of abs. THF under a nitrogen atmosphere and while cooling with ice and the mixture was stirred for 1 hour at RT. 1.1 g (4.43 mmol) of 2-chloro-4-chloromethyl-6-trifluoromethyl-phenylamine, dissolved in 10 mL abs. THF, was added dropwise and the mixture was stirred for 16 hours at RT. The reaction mixture was diluted with water and the aqueous phase extracted with EtOAc. The org. phase was dried over $MgSO_4$ and evaporated down i. vac.. The crude product was used in the next reaction step without any further purification.

Yield: 2.1 g (98% of theory)
ESI-MS: $(M+H)^+$ = 482/484 (Cl)
R_f = 0.48 (eluant: petroleum ether/EtOAc = 4/1)

2c) 4-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-3,3-bis-ethoxycarbonyl-butyric acid

20 mL of TFA was added to a solution of 30.0 g (62.25 mmol) of tert.butyl 4-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-3,3-bis-ethoxycarbonyl-butyrate in 200 mL CH_2Cl_2 while cooling with ice and the mixture was stirred for 16 hours at RT. The reaction mixture was evaporated down i. vac. and the

residue recrystallised from petroleum ether. The precipitate was filtered off, washed with petroleum ether and dried.

Yield: 23.6 g (89% of the yield)
ESI-MS: $(M-H)^-$ = 424/426 (Cl)

2d) diethyl 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-malonate

3.2 mL (23.0 mmol) of triethylamine was added dropwise to a solution of 8.00 g (19.0 mmol) of 4-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-3,3-bis-ethoxycarbonyl-butyric acid, 4.39 g (19.0 mmol) of 3-piperidin-4-yl-3,4-dihydro-1*H*-quinazolin-2-one, 6.00 g (18.0 mmol) of TBTU and 2.75 g (18.0 mmol) of HOBT in 100 mL of THF and the mixture was stirred for 16 hours at RT. The solid formed was filtered off, washed with diethyl ether and dried i. vac.

Yield: 10.45 g (87% of theory)

2e) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butyric acid

3.13 g (78.25 mmol) of NaOH, dissolved in 300 mL water, was added to a solution of 10.00 g (15.65 mmol) of diethyl 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-malonate in 600 mL EtOH and the mixture was refluxed for 4 hours. EtOH was evaporated off i. vac., the reaction mixture was acidified to pH 1 with conc. aqueous HCl and 1 hour at RT. The precipitate formed was filtered off, washed with water and dried i. vac..

Yield: 8.01 g (95% of theory)

2f) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(1'-methyl-[4,4']bipiperidinyl-1-yl)-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione

2.0 mL triethylamine was added to a solution of 0.80 g (1.48 mmol) of 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butyric acid, 0.28 g (1.50 mmol) of 1-methyl-[4,4']bipiperidinyl, 0.49 g (1.50 mmol) of TBTU and 0.23 g (1.50 mmol) of HOBT in 100 mL of THF and the mixture was stirred for 16 hours at RT. The reaction mixture was evaporated down i. vac., the residue was combined with saturated aqueous $NaHCO_3$ solution and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over $MgSO_4$ and evaporated down i. vac.. The residue was purified by column chromatography (silica gel, gradient of EtOAc/MeOH/conc. aqueous NH_3 = 94/5/1 → 70/25/5).

Yield: 253 mg (24% of theory)

ESI-MS: $(M+H)^+$ = 703/705 (Cl)

R_f = 0.66 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

Example 3

2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione

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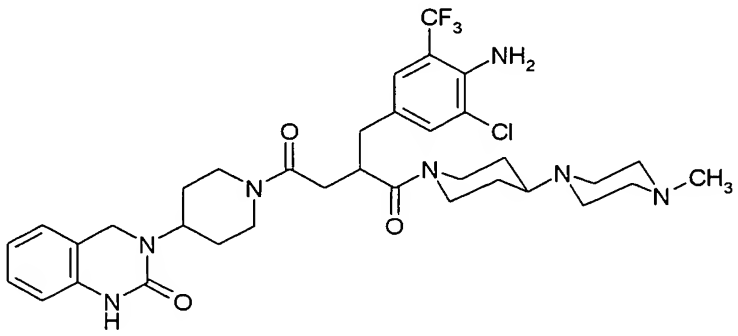


The product was obtained analogously to Example 2f) starting from 0.80 g (1.48 mmol) of 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butyric acid and 0.30 g (1.50 mmol) of 1-methyl-4-piperidin-4-yl-piperazine.

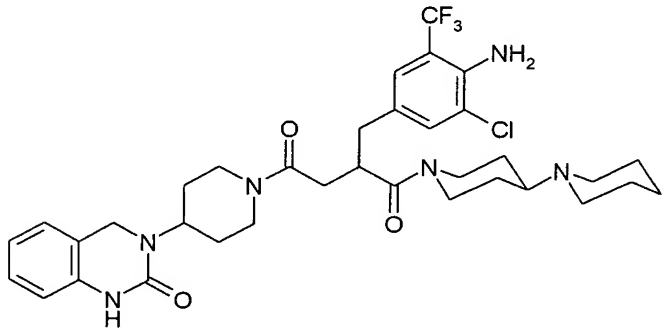
Yield: 600 mg (57% of theory)

EI-MS: M^+ = 703/705 (Cl)

R_f = 0.56 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

Example 4

2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione



The product was obtained analogously to Example 2f) starting from 0.80 g (1.48 mmol) of 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butyric acid and 0.27 g (1.50 mmol) of [1,4']bipiperidinyl.

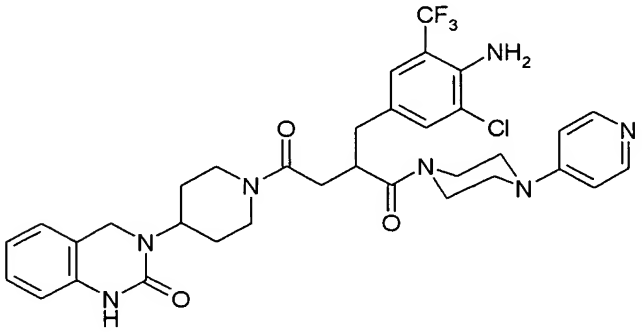
Yield: 240 mg (24% of theory)

ESI-MS: $(M+H)^+$ = 689/691 (Cl)

R_f = 0.59 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

Example 5

2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-1-(4-pyridin-4-yl-piperazin-1-yl)-butan-1,4-dione



The product was obtained analogously to Example 2f) starting from 0.80 g (1.48 mmol) of 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butyric acid and 0.24 g (1.48 mmol) of 1-pyridin-4-yl-piperazine.

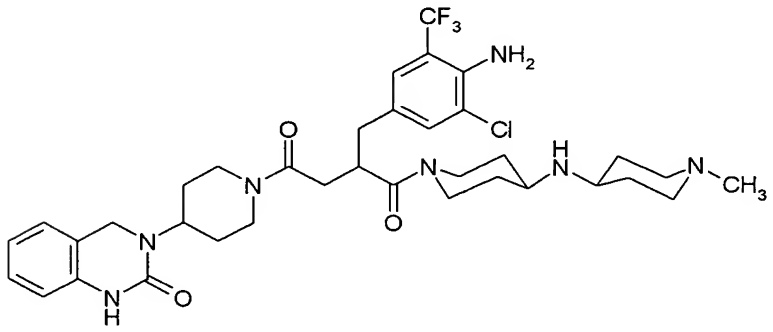
Yield: 500 mg (50% of theory)

EI-MS: M^+ = 683/685 (Cl)

R_f = 0.35 (eluant: MeOH)

Example 6

2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(1-methyl-piperidin-4-ylamino)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione



6a) (1-benzyl-piperidin-4-yl)-(1-methyl-piperidin-4-yl)-amine

A solution of 15.0 g (78.8 mmol) of 1-benzyl-piperidin-4-ylamine and 10 mL (78.8 mmol) of 1-methyl-piperidin-4-one in 300 mL of THF was acidified with HOAc to pH 5 and stirred for 1 hour at RT. 19.0 g (90.0 mmol) of sodium triacetoxyborohydride was added and the mixture was stirred for 16 hours. The mixture was evaporated down i. vac., the residue was dissolved in MeOH and precipitated by the addition of HCl in MeOH. The precipitate formed was filtered off, washed with MeOH and dried i. vac..

Yield: 21.8 g (70% of theory)

R_f = 0.30 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

6b) (1-methyl-piperidin-4-yl)-piperidin-4-yl-amine-trihydrochloride

A solution of 10.0 g (25.3 mmol) of (1-benzyl-piperidin-4-yl)-(1-methyl-piperidin-4-yl)-amine in 120 mL MeOH was added to a suspension of 5g of 10% Pd/C in 80 mL water and the mixture was hydrogenated for 2 hours at 50 °C under 3 bar. The reaction mixture was filtered and the filtrate was evaporated down i. vac.. The residue was combined with EtOH, the precipitate formed was filtered off, washed with EtOH and ether and dried i. vac..

Yield: 7.75 g (quantitative yield)

6c) 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(1-methyl-piperidin-4-ylamino)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione

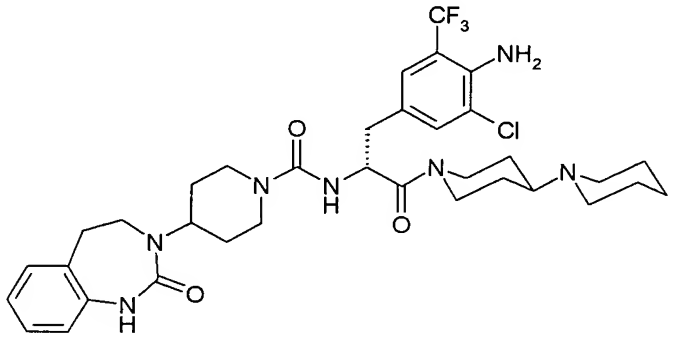
The product was obtained analogously to Example 2f) starting from 0.80 g (1.48 mmol) of 2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butyric acid and 0.24 g

(1.48 mmol) of (1-methyl-piperidin-4-yl)-piperidin-4-yl-amine-trihydrochloride.

Yield: 300 mg (25% of theory)
EI-MS: M^+ = 717/719 (Cl)
R_f = 0.20 (eluant: MeOH)

Example 7

4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carboxylic acid-[(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-1,4'-bipiperidinyl-1'-yl-2-oxo-ethyl]-amide



7a) (*R*)-2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-*N*-((1*S*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide

The alkylation was carried out in accordance with the general procedure described by A. G. Myers et al. (*J. Org. Chem.* **1999**, *64*, 3322-3327.) starting from 31.72 g (132 mmol) of 2-amino-*N*-((1S,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-acetamide-monohydrate and 33.8 g (138 mmol) of 2-chloro-4-chloromethyl-6-trifluoromethyl-phenylamine. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/ cyclohexane/MeOH/conc. aqueous NH_3= 70/15/15/2).

Yield: 10.0 g (18% of theory)
ESI-MS: $(M+H)^+$ = 430/432 (Cl)
R_f = 0.48 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

7b) (*R*)-2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionic acid

The hydrolysis was carried out in accordance with the general procedure described by A. G. Myers et al. (*J. Org. Chem.* **1999**, *64*, 3322-3327.) starting from 10.0 g (23.0 mmol) of (*R*)-2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-*N*-((1*S*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide. The crude product was used in the next synthesis step without any further purification.

7c) (*R*)-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-*tert*.-butoxycarbonylamino-propionic acid

A solution of 3.71 g (35.0 mmol) of $NaHCO_3$ in 100 mL water was added to a solution of 6.5 g (23.0 mmol) of (*R*)-2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionic acid in 140 mL of THF. 15.28 g (70.0 mmol) of Boc-anhydride was added and the mixture was stirred for 3 hours at RT. THF was evaporated off i. vac., the aqueous phase was washed with EtOAc and acidified with 10% aqueous citric acid. The aqueous phase was exhaustively extracted with EtOAc, the combined org. extracts were dried over Na_2SO_4 and evaporated down i. vac.. The crude product was used in the next reaction step without any further purification.

Yield: 2.00 g (15% of theory)
ESI-MS: $(M-H)^-$ = 381/383 (Cl)

7d) *tert*.-butyl [(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-carbaminate

1.53 mL (11.00 mmol) of triethylamine was added to a solution of 2.00 g (5.22 mmol) of (*R*)-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-*tert*.-butoxycarbonylamino-propionic acid, 0.99 g (5.30 mmol) of [1,4']bipiperidinyl, 1.77 g (5.50 mmol) of TBTU and 0.74 g (5.50 mmol) of HOBT in 150 mL of

THF and the mixture was stirred for 16 hours at RT. The reaction mixture was evaporated down i. vac., the residue was combined with saturated aqueous $NaHCO_3$ solution and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over $MgSO_4$ and evaporated down i. vac.. The residue was purified by column chromatography (aluminium oxide (neutral, activity III), CH_2Cl_2/MeOH = 99/1).

Yield: 500 mg (18% of theory)

7e) (*R*)-2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-1-[1,4']bipiperidinyl-1'-yl-propan-1-one-dihydrochloride

5 mL HCl (12 M in EtOH) was added at RT to a solution of 500 mg (0.75 mmol) of tert. butyl [(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-carbaminate in 50 mL EtOH and the mixture was stirred for 3 hours and then evaporated down i. vac.. The crude product was used in the next reaction step without any further purification.

Yield: 380 mg (quantitative yield)

7f) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carboxylic acid-[(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-1,4'-bipiperidinyl-1'-yl-2-oxo-ethyl]-amide

180 mg (1.10 mmol) of CDT was added at 0 °C to a solution of 380 mg (0.75 mmol) of (*R*)-2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-1-[1,4']bipiperidinyl-1'-yl-propan-1-one-dihydrochloride in 50 mL of DMF and 0.56 mL (4.00 mmol) of triethylamine and the mixture was stirred for 1.5 hours at 0°C. 242 mg (0.99 mmol) of 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one was added and the reaction mixture was stirred for 1.5 hours at 100 °C. DMF was evaporated off i. vac. and the residue was purified by column chromatography (silica gel, CH_2Cl_2/cyclohexane/ MeOH/conc. aqueous NH_3 = 70/15/15/2) followed by HPLC (silica gel RP18, gradient of acetonitrile/water 10/90 → 90/10).

Yield: 140 mg (20% of theory)

ESI-MS: $(M+H)^+$ = 704/706 (Cl)

R_f = 0.58 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

Example 8

4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carboxylic acid-[1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-1,4'-bipiperidinyl-1'-yl-2-oxo-ethyl]-amide

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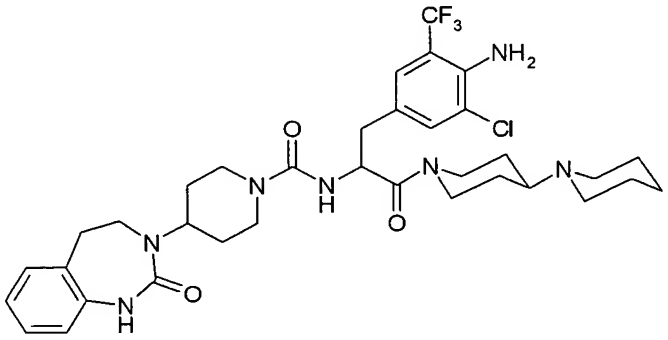


8a) diethyl 2-acetylamino-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-malonate

24.11 g (0.11 mol) diethyl 2-acetylamino-malonate was added to a freshly prepared solution of 2.55 g (0.11 mol) sodium in 200 mL abs. EtOH under a nitrogen atmosphere and the mixture was stirred for 15 minutes at RT. A solution of 27.00 g (0.11 mol) 2-chloro-4-chloromethyl-6-trifluoromethyl-phenylamine (Example 2a) in 100 mL of 1,4-dioxane was rapidly added dropwise and the mixture was stirred for 4 hours at RT. 500 mL of water were added and the mixture was stirred for a further 16 hours. The precipitate formed was filtered off, washed with water and dried i. vac..

Yield: 40.0 g (84% of theory)

R_f = 0.14 (eluant: petroleum ether/EtOAc = 2/1)

8b) 2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionic acid-hydrochloride

50 mL conc. aqueous HCl was added to a solution of 40.0 g (94.16 mmol) of diethyl 2-acetylamino-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-malonate in 110 mL AcOH and 150 mL of water and the reaction mixture was heated to 140 °C for 4 hours. The precipitate formed was filtered off and discarded. The filtrate was evaporated down i. vac., combined with 100 mL of EtOH and stirred for 15 minutes at RT. The precipitate formed was filtered off, washed with EtOH and dried i. vac.. The crude product was used in the next reaction step without any further purification.

Yield: 16 g (53% of theory)
ESI-MS: $(M-H)^-$ = 281/283 (Cl)

8c) ethyl 2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionate

16 g (50.14 mmol) of 2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionic acid-hydrochloride were dissolved in 350 mL of HCl (12 M in EtOH) and stirred for 5 hours at RT. The reaction mixture was evaporated down to 100 mL i. vac. and combined with 200 mL ether. The precipitate formed was filtered off, washed with ether and dried i. vac..

Yield: 12.2 g (70% of theory)
ESI-MS: $(M+H)^+$ = 311/313 (Cl)

8d) ethyl 3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-{[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carbonyl]-amino}-propionate

4.15 g (23.04 mmol) of CDT was added at 0 °C to a suspension of 8.00 g (23.04 mmol) of ethyl 2-amino-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-propionate and 16.0 mL (115.00 mmol) of triethylamine in 100 mL of DMF and

the mixture was stirred for 1.5 hours at 0 °C. A solution of 5.64 g (23.00 mmol) of 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one in 200 mL of DMF was added and the mixture was heated to 100 °C for 2 hours. The reaction mixture was cooled to RT, diluted with 1.5 L water and stirred for a further 10 minutes. The precipitate formed was filtered off, washed with water and dried i. vac..

Yield: 13.0 g (97% of theory)
ESI-MS: $(M+H)^+$ = 582/584 (Cl)

8e) 3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-{[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carbonyl]-amino}-propionic acid

45 mL of aqueous NaOH (1 M) were added to a solution of 13.00 g (22.34 mmol) of ethyl 3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-{[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carbonyl]-amino}-propionate in 100 mL EtOH and the mixture was stirred for 16 hours at RT. EtOH was evaporated off i. vac., 45 mL of aqueous HCl (1M) were added and the mixture was stirred for 15 minutes. The precipitate formed was filtered off, washed with water and dried i. vac. at 75 °C.

Yield: 10.5 g (85% of theory)
ESI-MS: $(M-H)^-$ = 552/554 (Cl)

8f) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carboxylic acid-[1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-1,4'-bipiperidinyl-1'-yl-2-oxo-ethyl]-amide

0.69 mL (5.00 mmol) of triethylamine was added to a solution of 1.00 g (1.81 mmol) of 3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-{[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-carbonyl]-amino}-propionic acid, 0.34 g (1.81 mmol) of [1,4']bipiperidinyl and 0.64 g (2.00 mmol) of TBTU in 150 mL of THF and the mixture was stirred for 16 hours at RT. The reaction

mixture was evaporated down i. vac., the residue was combined with saturated aqueous $NaHCO_3$ solution and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over $MgSO_4$ and evaporated down i. vac.. The residue was purified by column chromatography (silica gel, EtOAc/MeOH/ conc. aqueous NH_3 = 75/25/2.5).

Yield: 350 mg (28% of theory)

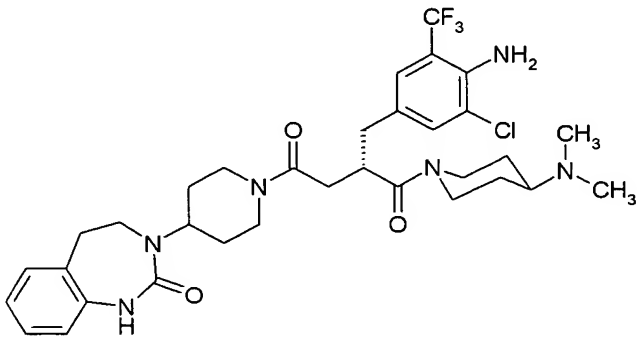
ESI-MS: $(M+H)^+$ = 704/706 (Cl)

R_f = 0.58 (eluant: CH_2Cl_2/cyclohexane/MeOH/conc. aqueous NH_3 = 70/15/15/2)

The following Examples may be prepared analogously to the methods described hereinbefore:

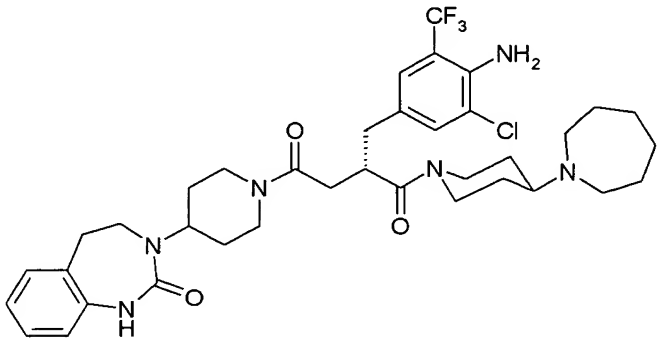
Example 9

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(4-dimethylamino-piperidin-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



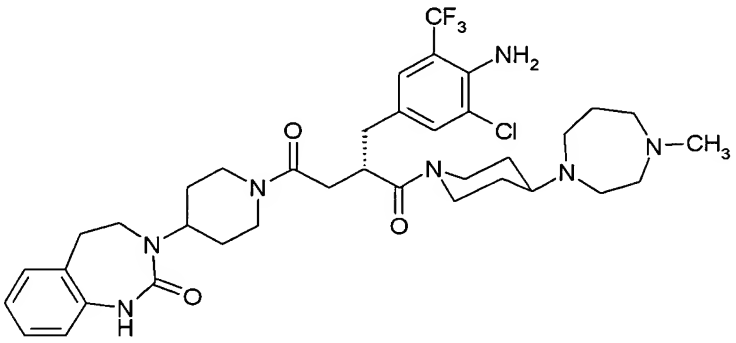
Example 10

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-perhydro-azepin-1-yl-piperidin-1-yl)-butan-1,4-dione



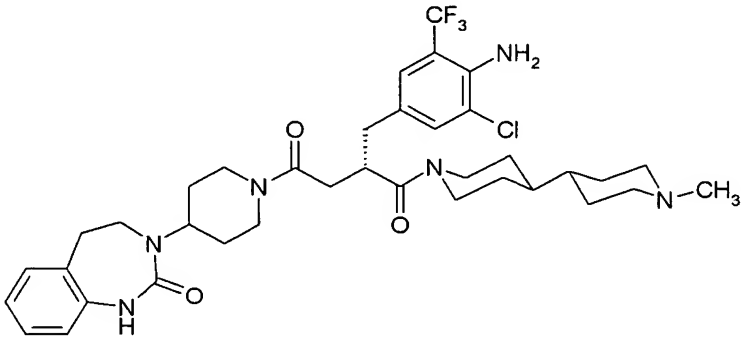
Example 11

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



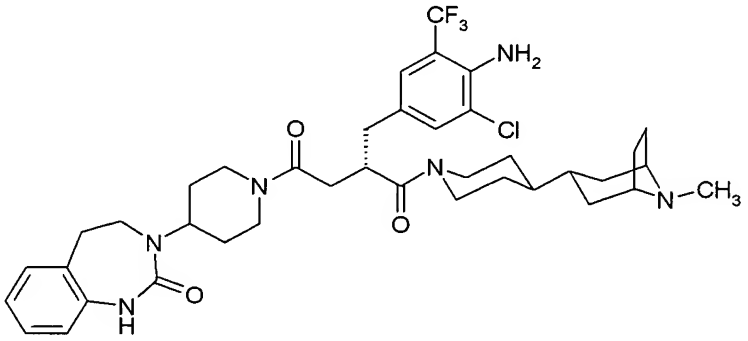
Example 12

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(1'-methyl-4,4'-bipiperidinyl-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



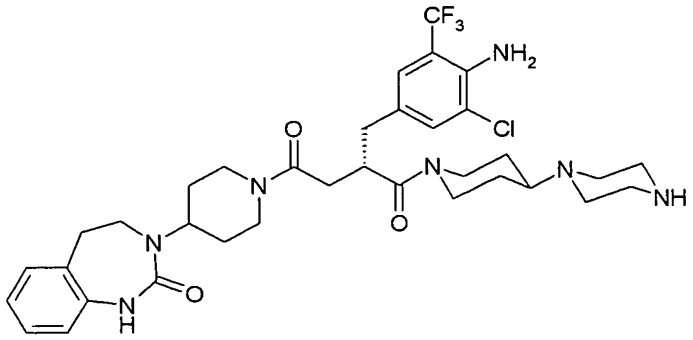
Example 13

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-piperazin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



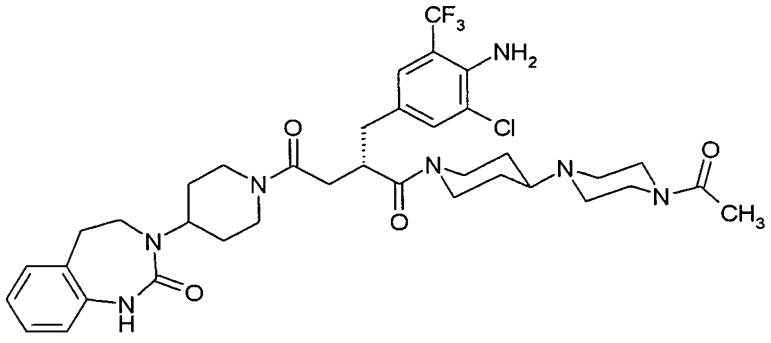
Example 14

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-piperazin-1-yl-piperidin-1-yl)-butan-1,4-dione



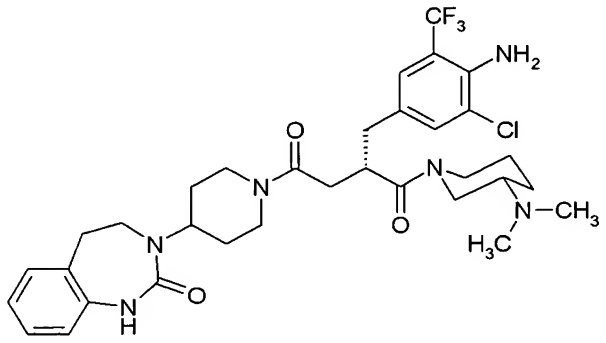
Example 15

(*S*)-1-[4-(4-acetyl-piperazin-1-yl)-piperidin-1-yl]-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



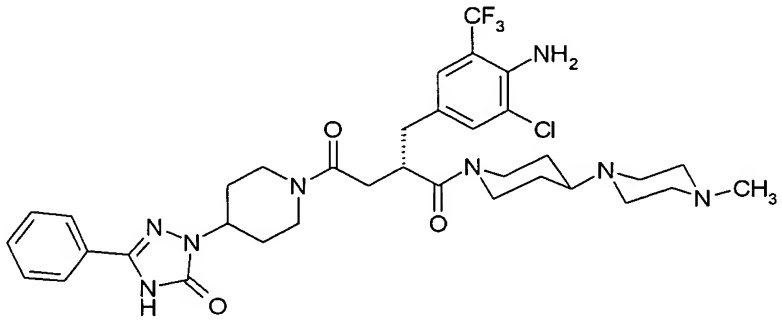
Example 16

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(3-dimethylamino-piperidin-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



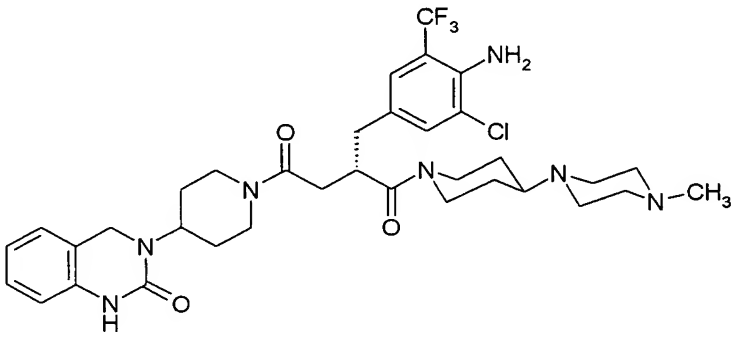
Example 17

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(5-oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)-piperidin-1-yl]-butan-1,4-dione



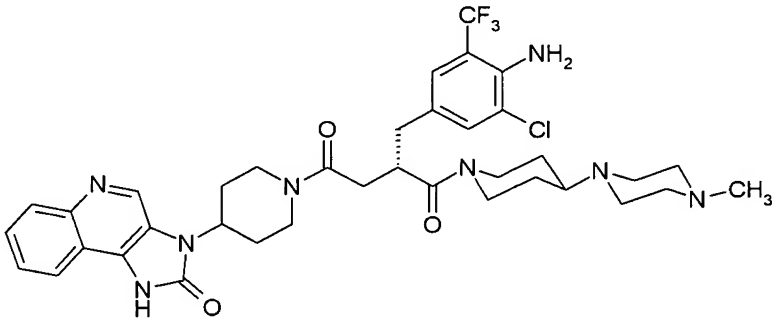
Example 18

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-butan-1,4-dione



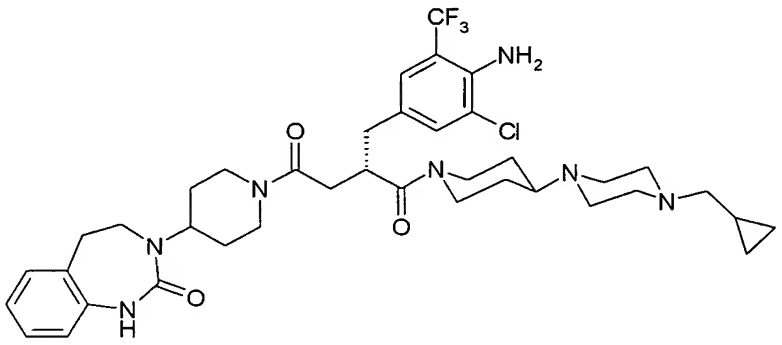
Example 19

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2-dihydro-imidazo[4,5-c]quinolin-3-yl)-piperidin-1-yl]-butan-1,4-dione



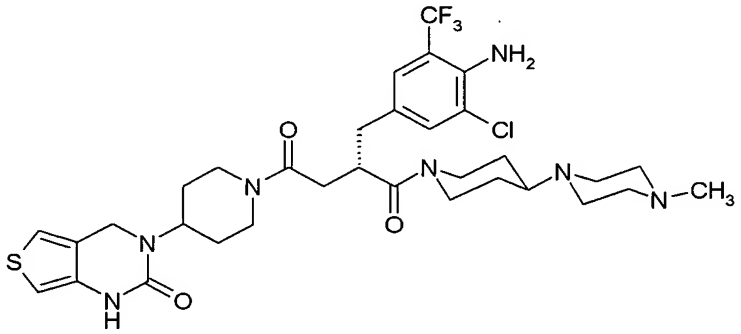
Example 20

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-cyclopropylmethyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



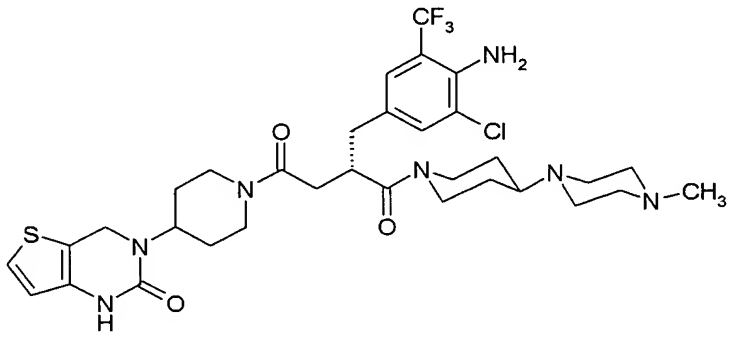
Example 21

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2-dihydro-4*H*-thieno[3,4-d]pyrimidin-3-yl)-piperidin-1-yl]-butan-1,4-dione



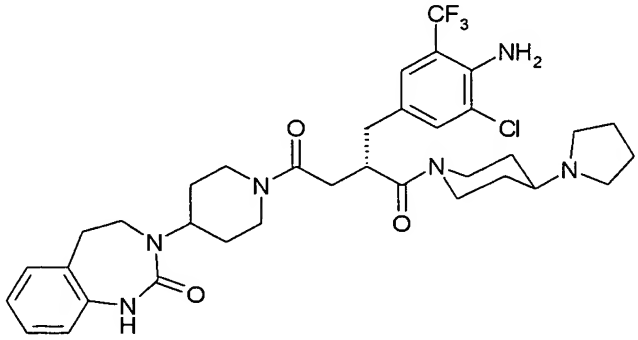
Example 22

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-thieno[3,2-d]pyrimidin-3-yl)-piperidin-1-yl]-butan-1,4-dione



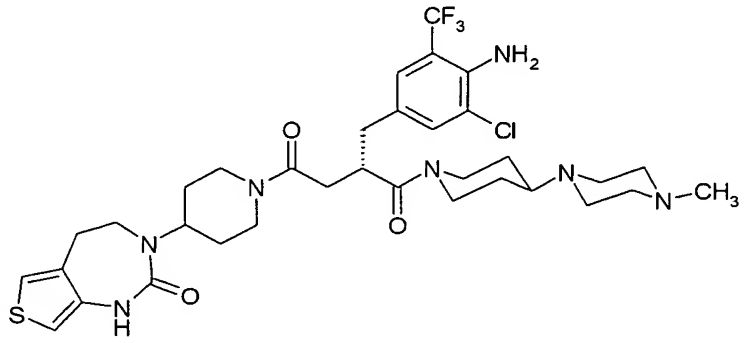
Example 23

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-pyrrolidin-1-yl-piperidin-1-yl)-butan-1,4-dione



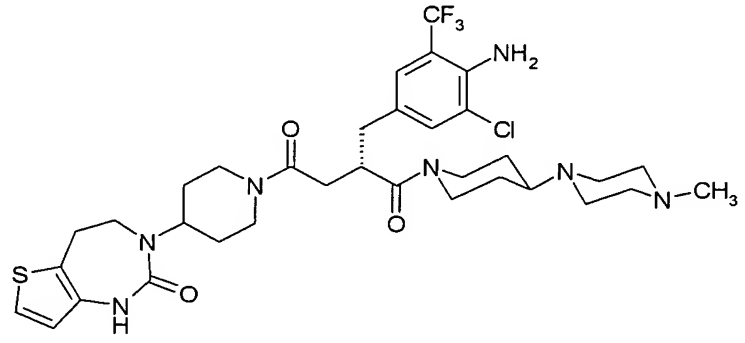
Example 24

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(5-oxo-4,5,7,8-tetrahydro-2-thia-4,6-diaza-azulen-6-yl)-piperidin-1-yl]-butan-1,4-dione



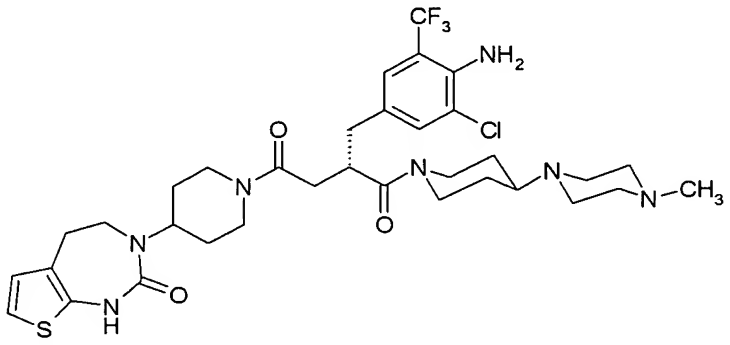
Example 25

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-thieno[3,2-d]-1,3-diazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



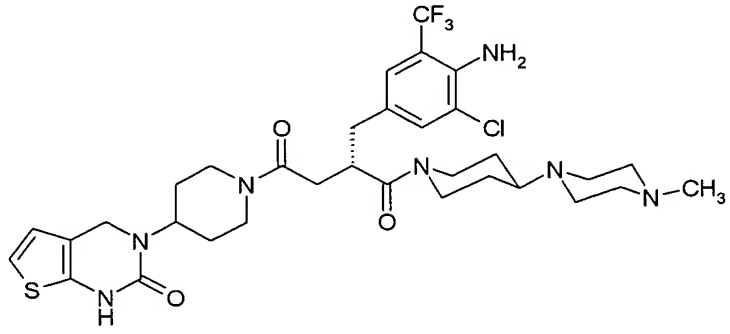
Example 26

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-thieno[2,3-d]-1,3-diazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



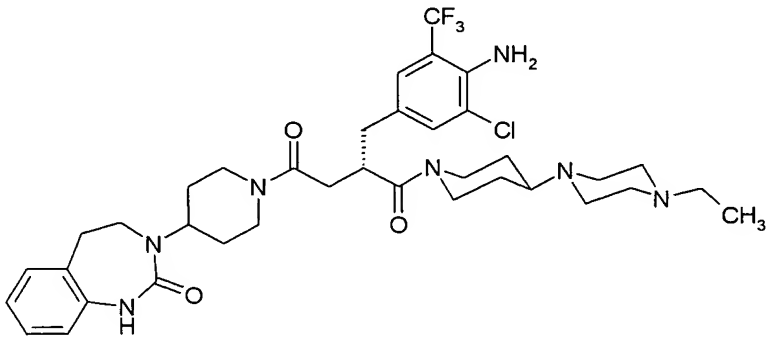
Example 27

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,4-dihydro-2*H*-thieno[2,3-d]pyrimidin-3-yl)-piperidin-1-yl]-butan-1,4-dione



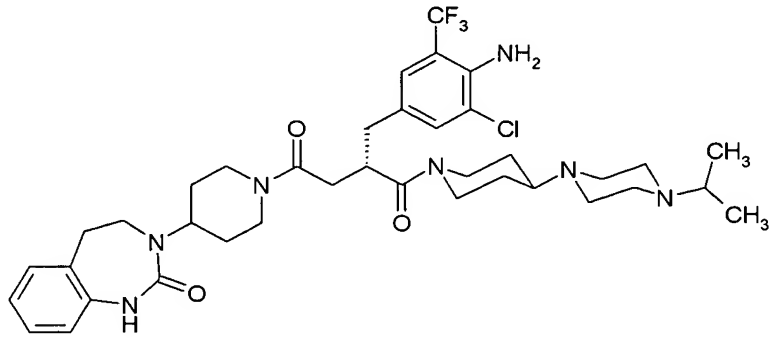
Example 28

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-ethyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



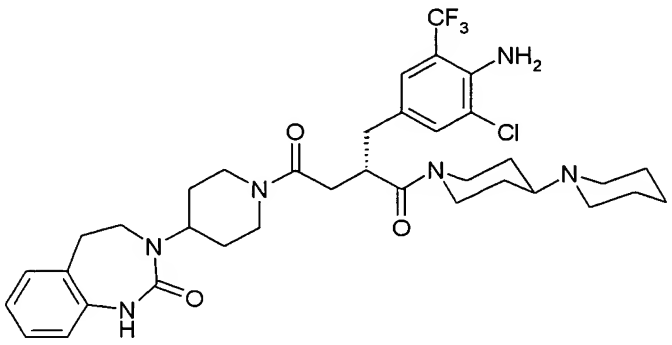
Example 29

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-isopropyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



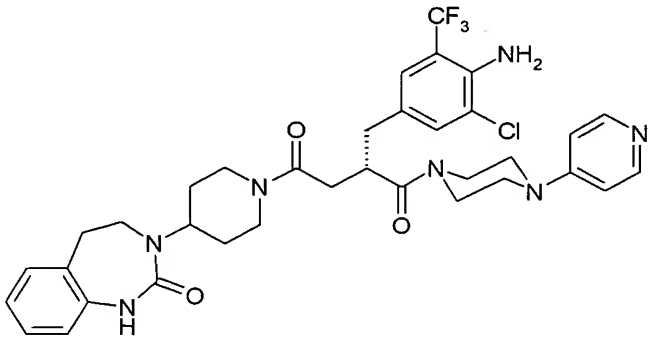
Example 30

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-1,4'-bipiperidinyl-1'-yl-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



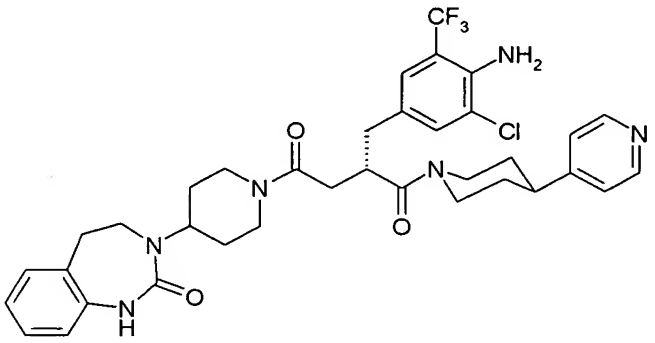
Example 31

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(4-pyridin-4-yl-piperazin-1-yl)-butan-1,4-dione



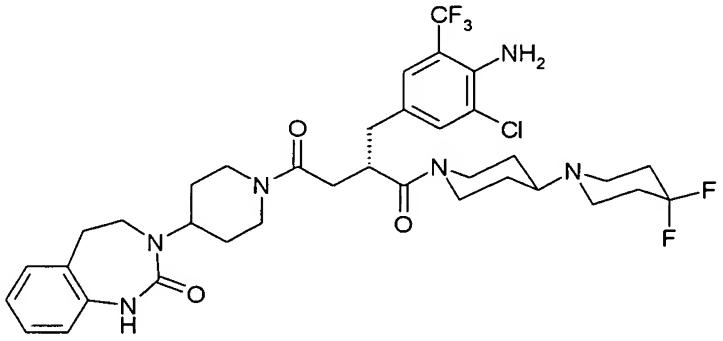
Example 32

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-1-(3,4,5,6-tetrahydro-2*H*-4,4'-bipyridinyl-1-yl)-butan-1,4-dione



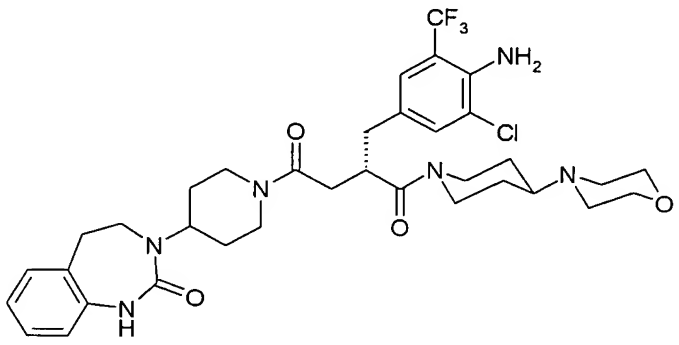
Example 33

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(4,4-difluoro-1,4'-bipiperidinyl-1'-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



Example 34

(*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-(4-morpholine-4-yl-piperidin-1-yl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butan-1,4-dione



The following Examples describe the preparation of pharmaceutical formulations which contain as active substance any desired compound of general formula (I):

Example I

Capsules for powder inhalation containing 1 mg of active ingredient

Composition:

1 capsule for powder inhalation contains:

active ingredient	1.0 mg
lactose	20.0 mg
hard gelatine capsules	50.0 mg
	71.0 mg

Method of preparation:

The active ingredient is ground to the particle size required for inhaled substances. The ground active ingredient is homogeneously mixed with the lactose. The mixture is transferred into hard gelatine capsules.

Example II

Inhalable solution for Respimat® containing 1 mg of active ingredient

Composition:
1 puff contains:

active ingredient	1.0 mg
benzalkonium chloride	0.002 mg
disodium edetate	0.0075 mg
purified water ad	15.0 µl

Method of preparation:
The active ingredient and benzalkonium chloride are dissolved in water and transferred into Respimat® cartridges.

Example III

Inhalable solution for nebulisers containing 1 mg of active ingredient

Composition:
1 vial contains:

active ingredient	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water ad	20.0 ml

Method of preparation:
The active ingredient, sodium chloride and benzalkonium chloride are dissolved in water.

Example IV

Propellant gas-operated metering aerosol containing 1 mg of active ingredient

Composition:

1 puff contains:	
active ingredient	1.0 mg
lecithin	0.1 %
propellant gas ad	50.0 µl

Method of preparation:

The micronised active ingredient is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

Example V

Nasal spray containing 1 mg of active ingredient

Composition:

active ingredient	1.0 mg
sodium chloride	0.9 mg
benzalkonium chloride	0.025 mg
disodium edetate	0.05 mg
purified water ad	0.1 ml

Method of preparation:

The active ingredient and the excipients are dissolved in water and transferred into a suitable container.

Example VI

Injectable solution containing 5 mg of active substance per 5 ml

Composition:	
active substance	5 mg
glucose	250 mg
human serum albumin	10 mg
glycofurol	250 mg
water for injections ad	5 ml

Preparation:

Glycofurol and glucose are dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules under nitrogen gas.

Example VII

Injectable solution containing 100 mg of active substance per 20 ml

Composition:	
active substance	100 mg
monopotassium dihydrogen phosphate = KH_2PO_4	12 mg
disodium hydrogen phosphate = $Na_2HPO_4 \cdot 2H_2O$	2 mg
sodium chloride	180 mg
human serum albumin	50 mg
Polysorbate 80	20 mg
water for injections ad	10 ml

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules.

Example VIII

Lyophilisate containing 10 mg of active substance

Composition:

Active substance	10 mg
Mannitol	300 mg
human serum albumin	20 mg
water for injections ad	2 ml

Preparation:

Mannitol is dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into vials; freeze-dried.

Solvent for lyophilisate:

Polysorbate 80 = Tween 80	20 mg
mannitol	200 mg
water for injections ad	10 ml

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (WfI); transferred into ampoules.

Example IX

Tablets containing 20 mg of active substance

Composition:

active substance	20 mg
lactose	120 mg
maize starch	40 mg
magnesium stearate	2 mg
Povidone K 25	18 mg

Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

Example X

Capsules containing 20 mg active substance

Composition:

active substance	20 mg
maize starch	80 mg
highly dispersed silica	5 mg
magnesium stearate	2.5 mg

Preparation:

Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example XI

Suppositories containing 50 mg of active substance

Composition:	
active substance	50 mg
hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

Example XII

Injectable solution containing 10 mg of active substance per 1 ml

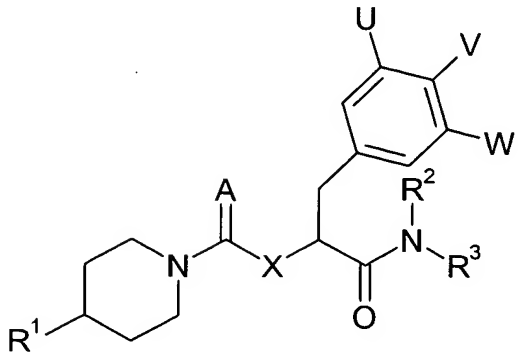
Composition:	
active substance	10 mg
mannitol	50 mg
human serum albumin	10 mg
water for injections ad	1 ml

Preparation:

Mannitol is dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules under nitrogen gas.

Abstract

The present invention relates to CGRP antagonists of general formula



, (I)

wherein A, U, V, W, X and R^1 to R^3 are defined as in claim 1,

the tautomers, diastereomers, enantiomers, hydrates, mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids, pharmaceutical compositions containing these compounds, the use thereof and processes for preparing them.